A 5 year retrospective study of spectrum of Cutaneous Lymphomas presenting to a Tertiary Care Centre

A dissertation submitted to the Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of M.D. (Branch –III) (General Pathology)

APRIL 2015

CERTIFICATE

This is to certify the dissertation entitled, "A 5 year retrospective study of spectrum of Cutaneous Lymphomas presenting to a Tertiary Care Centre" is the bonafide work of Dr. Jigar Kiritkumar Shah toward the M.D (Branch –III General Pathology) Degree examination of the Tamil Nadu Dr.M.G.R Medical University, to be conducted in April 2015.

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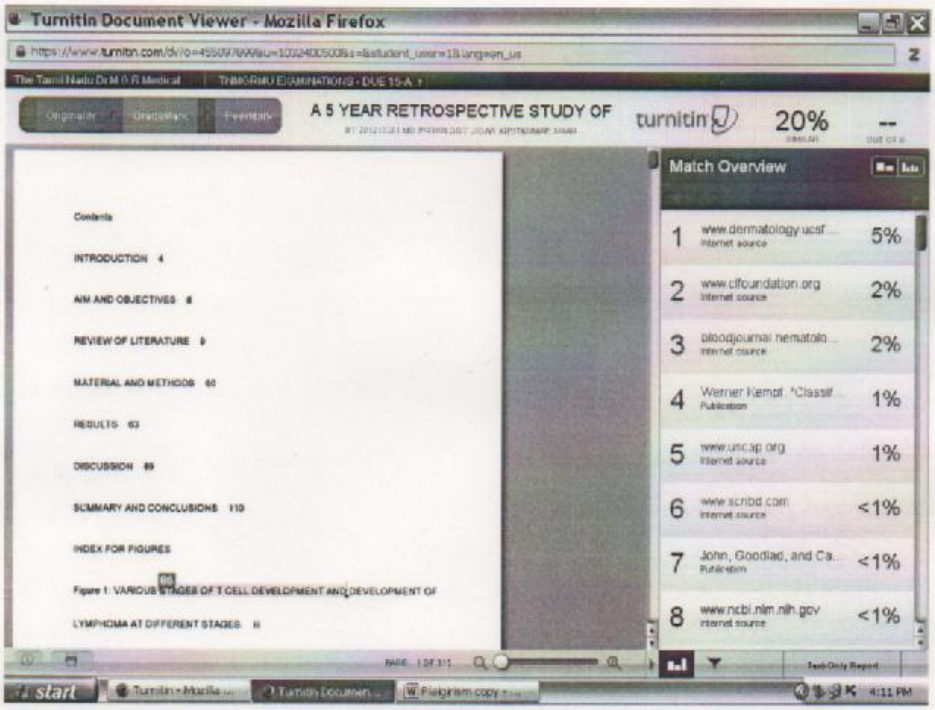
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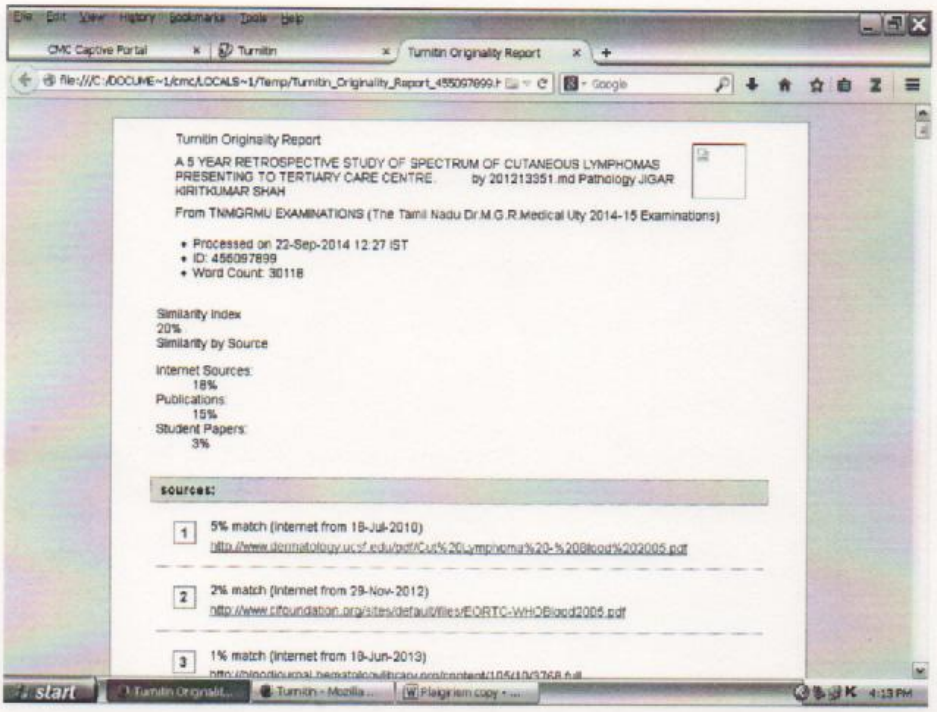

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A 5 YEAR RETROSPECTIVE STUDY OF SPECTRUM OF CUTANEOUS LYMPHOMAS PRESENTING TO TERTIARY CARE CENTRE. by 201213351.md Pathology JIGAR KIRITKUMAR SHAH

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The Author

Contents

ABSTRACT

TITLE OF THE ABSTRACT: A 5 year retrospective study of spectrum of cutaneous lymphoma presenting to a Tertiary Care Centre.

DEPARTMENT: General Pathology.

NAME OF THE CANDIDATE: Dr. Jigar Kiritkumar Shah

DEGREE AND SUBJECT: M.D. {GENERAL PATHOLOGY}

NAME OF THE GUIDE: Dr. Meera Thomas

OBJECTIVES: To ascertain frequencies of different cutaneous lymphomas and their correlation with clinical and laboratory parameters as well as to check the role of new markers Notch-1 and Foxp1 in prognostication.

METHODS: This 5 year study was carried out in the Department of General Pathology, Christian Medical College and Hospital, Vellore, India. The histopathological materials were accrued from the archives of the department. The clinical information and laboratory parameters were obtained from clinical workstation and charts from medical records department or from the biopsy request forms for outside referral cases.

Data entry and statistical analysis were done using Epi-info software. Descriptive statistics such as frequency and percentage were used. Categorical variables were analyzed using $\chi 2$ test and Fischer's exact test. A p value of < 0.05 was considered statistically significant.

RESULTS: Totally 115 patients were enrolled in the study with a mean age of 39 years and male predominance. The presenting age was lower than documented earlier, with Mycosis Fungoides (MF) {44%} being the commonest cutaneous lymphoma followed by Subcutaneous panniculitis like T cell lymphoma {21%}. There were increased numbers of hypopigmented MFs (53%), in juvenile cases where females were predominant. The frequency and clinical/laboratory parameters of other T cell lymphomas were comparable to literature. We had increased numbers of cutaneous B cell lymphoma, other type {3.5%}. International Prognostic Index, FoxP1 and Notch-1 were associated with prognosis.

Key words: Mycosis Fungoides, Hypopigmented Mycosis Fungoides Notch-1, Fox p1.

INTRODUCTION

Lymphomas constitute approximately 6.1% and 3.1% of all malignancies worldwide and India respectively (1–4). Among the lymphomas the Non Hodgkin lymphomas {NHL} are more common than Hodgkin lymphomas. Out of all extra-nodal Non Hodgkin lymphomas (NHLs), the skin is the second most common site after gastrointestinal tract with a yearly incidence of 1:10000(2). In various studies the documented frequencies of cutaneous lymphomas were 1-2% and 10-15% of all lymphomas and extra nodal Non-Hodgkin lymphoma respectively (2,5).

Primary cutaneous lymphomas {PCLs} includes cutaneous T cell lymphomas {CTCLs}, cutaneous B cell lymphomas {CBCLs} and Blastic dendritic cell neoplasm {BDCN}, that involves the skin without evidence of extracutaneous involvement, at the time of diagnosis(2,6).

The incidence of primary cutaneous lymphomas is vary with race, age, gender and geographic location (7). A study by Wilson et al. has shown higher incidence of PCLs in African-Americans and elderly male patients (7). The Asian ethnical origin population was involved at younger age as documented in similar study {For non-Mycosis Fungoides PCLs} (7).

In comparison to lymphomas elsewhere in the body where B cell lymphomas are more common than T cell lymphomas, the cutaneous T cell lymphomas comprised 75-80% of all cutaneous lymphomas (6, 8). In a study incorporating WHO-EORTC classification from the Dutch and Austrian registry, T cell lymphomas and B cell lymphomas constituted about 76% and 24% of the primary cutaneous lymphomas respectively (6). A higher incidence of SPTCL and NK/T cell lymphomas have been reported in India (15-19%)(3,4) and many Far East Countries respectively(17-30%)(9,10)

Mycosis fungoides (MF) is the most common primary cutaneous lymphoma, the incidence of which varies in different populations {higher in African American and black male population} (2,7,11). This lymphoma constituted 40-45% of all cutaneous lymphomas as documented in Western literature, standard textbooks and major published studies (2,6). MF formed 2-10% of peripheral T cell lymphomas (2, 5). In a 10 year study done in south India the frequency of MF was 36% out of all cutaneous lymphomas{11 of 31 cases}(12). Another study done from the same center on 180 patients showed that the frequencies of cutaneous lymphomas and peripheral T cell lymphomas (PTLs) were 35% and 11.6% respectively (13)

Different subtypes of MF has been documented in standard textbooks and WHO-EORTC classification based on morphology and immunophenotype like folliculotropic, pagetoid reticulosis and granulomatous slack skin(2,6).

Subcutaneous panniculitis T cell lymphomas (SPTCLs) are uncommon types of PCTLs with a higher frequency in Far East countries and India (2,6) as compared to the Western population(6,14).

CD30 positive lymphoproliferative disorders are classified further in Lymphomatoid papulosis (LyP) and anaplastic large cell lymphoma (ALCL) (6). Morphologically these lymphomas are more heterogeneous as compared to other T lymphomas and hence are difficult to diagnose and usually requires detailed clinical history and immunohistochemistry study (2,6).

The classification of remaining T cell lymphomas is difficult due to its rarity and heterogeneity. This group comprised approximately 10% of CTCLs (15). These lymphomas are aggressive and in majority of cases require systemic chemotherapy (2).

The primary cutaneous B cell lymphomas (PCBCLs) categorize in primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B cell lymphoma (PCDLBCL)(2,6,16). The latter category included three more subtypes, PCDLBCL-leg type, Intra vascular large B cell lymphoma and PCDLBCL, other (2). There was continuous debate for this category as morphology, prognosis and therapy differs for latter two categories {PCFCL and PCDLBCL}. PCDLC-leg type was initially identified under PCFCL with different histology and more unfavorable prognosis. It primary affect elderly female patient with higher relapse rate (2). Before making diagnosis of primary cutaneous B cell lymphoma always exclude metastasis from nodal B cell lymphoma, as secondary involvement of skin is more common than primary cutaneous B cell lymphoma(2).

The classification for cutaneous lymphomas have undergone many modifications with new entities added over the years (2, 5, 6). Although it was initially proposed to apply the Revised European American classification (REAL) for cutaneous lymphoma also, this was abandoned as this classification was found to be less promising than European Organization for Research and Treatment of Cancer (EORTC) classification{due to easy clinical applicability and good correlation with prognosis}(6). The WHO classification was based on the REAL classification and included histomorphology, immunophenotyping, clinical features and genotyping. Both classifications were superior in their own ways, however there were many shortcomings that lead to continuous debate (2, 6). After an agreement during meetings held in 2003 and 2004, representatives from both organizations designated a new classification for cutaneous lymphomas named WHO-EORTC classification {Appendix 7} (6)

AIM AND OBJECTIVES

AIM:

To determine the relative frequency of cutaneous lymphomas, its correlation with Immunohistochemistry and with clinical diagnosis, reclassify them according to the new WHO-EORTC Classification (2005) and modified classification in 2008(6).

OBJECTIVES:

I) To ascertain the frequencies and types of cutaneous lymphomas diagnosed in Christian Medical College Hospital (CMCH) during a period of 5 years (from 01/05/2007 to 31/05/2012).

II) To study and correlate the morphology and immunohistological profile of these cutaneous lymphomas and sub-classify them according to the WHO/EORTC classification (2005) and its modification in 2008(6).

III) To study the symptoms, duration of illness, clinical presentation(macules, papules, nodules etc.), organomegaly, lymphadenopathy and laboratory parameters(HB, TC, DC, Platelets, ESR, LDH level, Bone marrow study and TCR rearrangement whenever available) of the cases and to correlate them with morphological subtypes.

IV) To study the usefulness of new markers (NOTCH1 and FOXp1) and its role in diagnosis, prognosis and categorization of cutaneous lymphomas. The outcome of treatment is also correlated with these new markers (whether patient improved, deteriorated or died).

REVIEW OF LITERATURE

Primary cutaneous lymphomas comprise a group of lymphomas involving the skin without evidence of extra cutaneous disease at the time of presentation (6).They are of 2 types - primary T cell lymphomas (PTLs) and primary B cell lymphomas (PBCLs).

Skin is the second most common site for extra nodal non-Hodgkin's lymphoma after the gastrointestinal tract with an annual incidence of 1:100000(1).A complied data published byWillemze R et al., in Leiden University Center,The Netherlands, based on 1905 primary cutaneous lymphoma patients registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986-2002showed that Mycosis fungoides was the most common cutaneous lymphoma whichcomprised 50% of all primary cutaneous lymphomas (17)**.**

The denomination "cutaneous T-cell lymphoma" (CTCL) was used for the first time in 1975 to include MF and its variants, and it later included other Primary cutaneous lymphoma(PCL) types and the spectrum of CD30 positive PCLs, primary subcutaneous panniculitis-like T-cell lymphomas, nasal-type NK/T-cell PCL, and non-classifiable T-cell PCL(18).

In 2007, the International Society for Cutaneous Lymphoma (ISCL) and the EORTC published a review of the staging and specific classification of MF and SS {Table 3}. The review modified the staging system and provided an accurate definition of SS, in particular (19).

PCLs have been classified into distinct subtypes according to the WHO 2005(modified-2008) classification {Appendix 7}.The comparison between two classifications is enlisted in Appendix 12.

Apart from the morphology; Immunohistochemistry and molecular studies including T cell receptor rearrangement studies play an important role in the diagnosis of lymphomas.

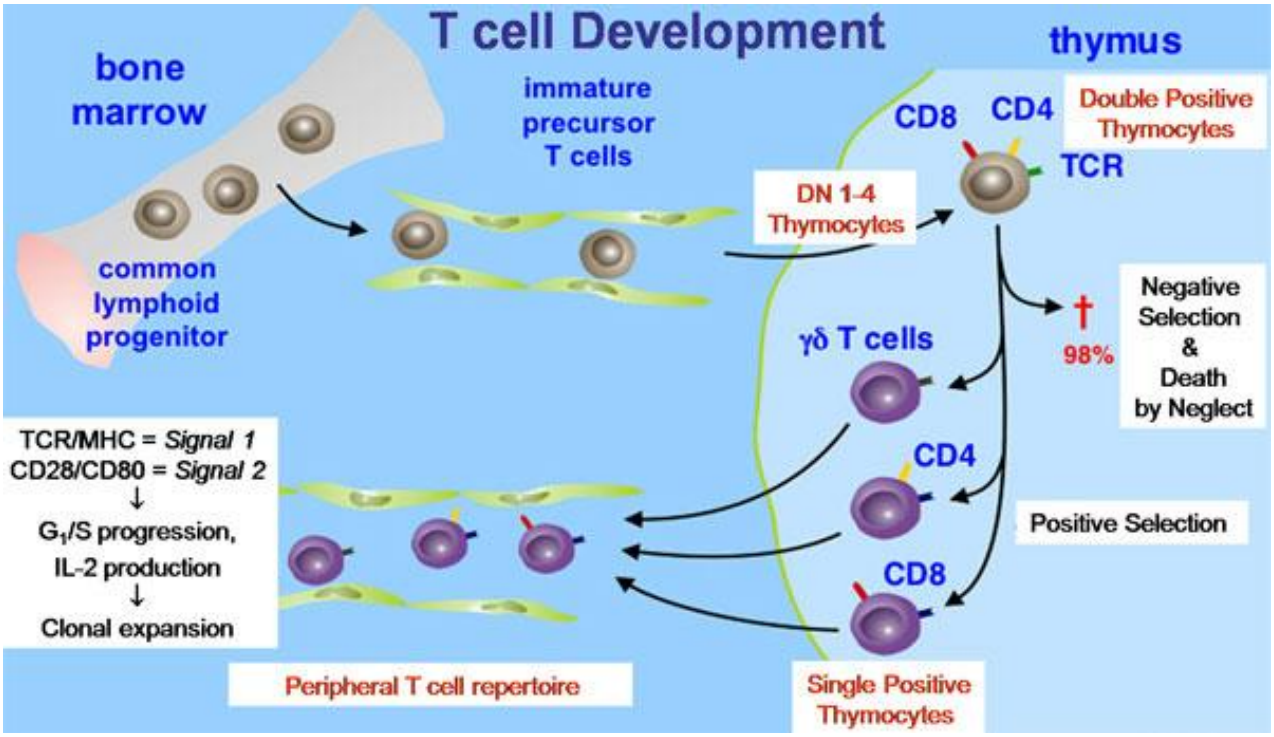
IMMUNOHISTOCHEMISTRY:

Immunohistochemistry plays a very important role in the diagnosis of lymphomasboth cutaneous T and B cell lymphomas {Appendix 13&14}.

T cell development and different Cluster Designation: Primary T cell lymphomas are more common than B cell lymphomas. The type of T cell lymphoma follows the maturation of the T lymphocyte(20). CD7 is the earliest T cell antigen expressed from the prothymocyte stage along with TdT {terminal deoxynucleotidyltransferase}. Expression of CD2, CD5 and then CD3 follows CD7. Expression of CD3 is cytoplasmic {CD3 epsilon} in the beginning upto the cortical thymocyte stage and thereafter surface expression is seen. Expression of the subset antigens CD4 and CD8 begins at the immature cortical thymocyte stage and these are double positive as shown in {Appendix 5}. As the lymphocytes mature they express either CD4 or CD8 alone.

CD4+ T cells are those T helper cells which do not express cytotoxic granule associated protein TIA-1 {T cell restricted intracellular antigen 1}, whereas it is expressed by CD8+ T-suppressor/cytotoxic cells. The immunohistochemical findings which point towards a diagnosis of PTCLs are presence of a markedly abnormal CD4/CD8 ratio (in the absence of HIV or other viral infection), aberrant loss of pan–T-cell antigens (CD2, CD3, CD5, CD7), lack of CD4 and CD8, or dual expression of CD4 and CD8{Figure 1}

Figure 1: VARIOUS STAGES OF T CELL DEVELOPMENT AND DEVELOPMENT OF LYMPHOMA AT DIFFERENT STAGES.

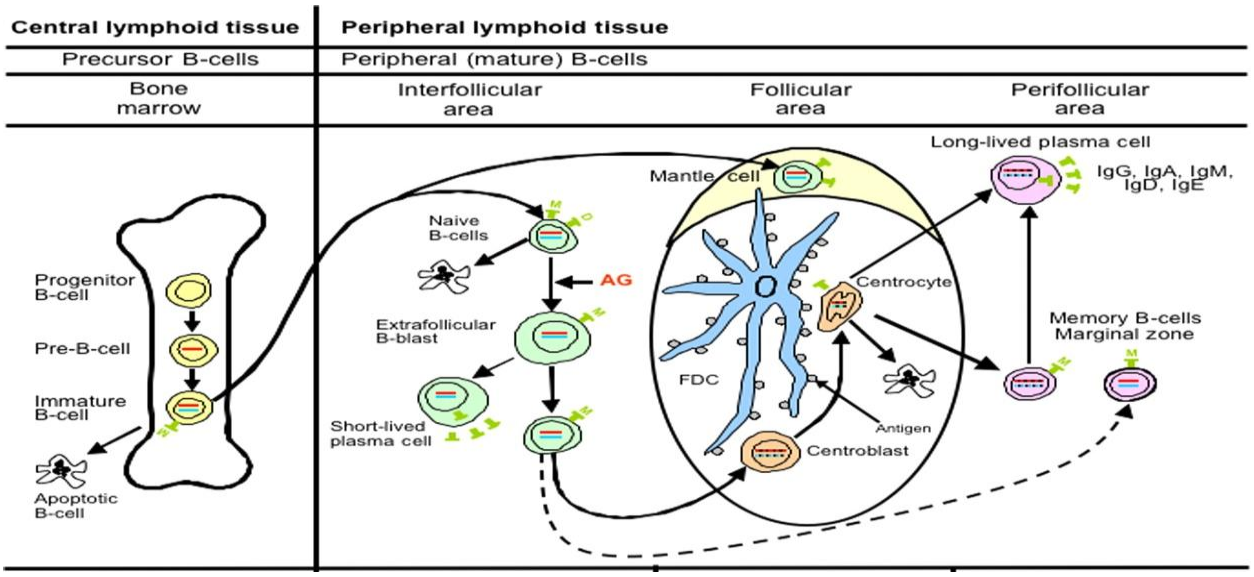


(Adapted and modified from: Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood 2008 Dec 1;112(12):4384–99)

B cell development and different Cluster Designation: Similar to T cell neoplasms, B-cell neoplasms correspond to stages of B-cell maturation. The bone marrow is the primary site where precursor B cells mature and they may undergo cell programmed death or develop into mature naive B cells (20). Following exposure to antigen and blast transformation, these cells may convert into short lived plasma cells or enter the germinal center (GC), where somatic hypermutation and class switching of heavy chain occur (20). The transformed cells of germinal center, centroblasts, either undergo apoptosis or develop into centrocytes. Post germinal center cells include both plasma cells and memory/marginal zone B cells. Activation of most B cells is within the GC, but T cell independent activation can take place outside of the germinal

center that leads to memory-type B cells. The development of B cell and different CDs expressed at different levels is shown in Figure 2. The various immunohistochemical markers used for the diagnosis of PCL are described (20) in detail in Appendix 5&6.

Figure 2: VARIOUS STAGES OF B CELL DEVELOPMENT



(Adapted from: Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008 Dec 1;112(12):4384–99)

T cell receptor rearrangement (21)

T cell receptors are heterodimers consisting of either α/β or γ/δ chains. At early stages of T cell maturation in thymus, the T cell receptor loci {TCR} are subjected to a process called V/D/J recombination. PTCL arise from T cells that undergo malignant transformation after most rearrangements of TCR loci are completed. Thus identification of clonal cells with identical rearrangement favors a diagnosis of malignancy. TCR-γ is a favorite target for T cell clonality assessment as it has a relatively simple structure and it is rearranged before α and β chains. T

cell clonality is usually assessed by Southern blotting or polymerase chain reaction {PCR} with subsequent detection of amplification products by various techniques such as single-strand conformation polymorphism (SSCP) analysis, denaturing gradient polyacrylamide gel electrophoresis, heteroduplex analysis, and fragment analysis using the Genescan method (21).

CLINICOPATHOLOGIC PROFILE OF THE MAIN SUBTYPES OF PRIMARY CUTANEOUS LYMPHOMAS:

CUTANEOUS T CELL LYMPHOMAS:

MYCOSIS FUNGOIDES (MF)

By definition “Mycosis fungoides” {MF} is a primary cutaneous T cell lymphoma with epidermotropism and is characterized by infiltrates of small to medium sized T lymphocytes with cerebriform nuclei (8).

This term should be restricted to what is described by Alibert-Bazin with different stages of evolution from patches to plaque and tumor which included MF and its systemic variant Sézary syndrome (SS) characterized by clonal proliferation of CD 4 and CD45RO positive memory T-cells and aberrant loss of mature T cell antigens(6).

History of MF: In 1806, MF was first described in France by Alibert, who named it in 1814 as "Pian fungoides"(22). The term "mycosis fungoides" was only adopted by Alibert in 1832(6). In 1870, Bazin described its evolution according to the natural history of the disease and defined its stages(23). Such a description is classic and has been used to this date: patch, plaque, tumoral and systemically disseminated (6).

In 1892, the erythrodermic form of MF was described. It is characterized by erythema, scaling and generalized infiltration of the skin. In 1938, the description of Sézary syndrome was made(6). "Pagetoid reticulosis" was described in 1931 as "Ketron-Goodman's disease"(24), which would correspond to the generalized form of pagetoid reticulosis, and, in 1939, solitary hyperkeratosis was described by Woringer-Kolopp (25). The Ketron-Goodman subtype is no longer considered pagetoid reticulosis and probably corresponds to the aggressive epidermotropic CD8+ cutaneous T-cell lymphoma (26).

Frequency: This tumor comprises about 2-10% of all the PTCLs(3,4,9,11,27,28) and is the most common primary T cell lymphoma primarily involving the skin comprising about 55% of the cases (29)in western study and 60-70% in Indian studies(12,30) .

Epidemiology and trend of progression: A study from Texas on 1263 patients of MF and Sézary syndrome showed the mean age of diagnosis was 55.3 years (31). In the same study which comprised predominantly early MF patients (71.5%), the male to female ratio was almost same (31). A registry based study in US showed the incidence of MF was 0.29/100000 per year and incidence increased over the period of 10 year study. Blacks were affected twice as common as white. The incidence was higher in elderly (32). Another study from Spain showed the risk of Mycosis fungoides was higher in males and in blacks (33). A study from Israel during the period of 1985-93 showed the incidence rate of cutaneous lymphomas (CL) [including mycosis fungoides (MF) and non-mycosis fungoides (non-MF)] were 1.18 and 0.63 for Jewish men and women respectively(34). For Non-Jews the rates were significantly lower (34). A study from Norway, in which totally 337 cases of cutaneous T cell lymphomas were reported to the Cancer

Registry during the study period of 23 years (1980-2003), of which 262 cases were classified as MF/SS. The incidence of MF/SS as well as other cutaneous lymphomas had increased during the same period (35).

In India, MF/SS is an extremely rare neoplasm (36). A tertiary care center from South India reported only 20 cases(out of 31) of MF/SS over 10 years, out of which 1 patient was serologically positive for human T-cell leukemia virus type 1(12). Mycosis fungoides was the most common CTCL (55.5%)(12).

Etiology: The etiology of MF is obscure. Several aetiopathogenetic mechanisms including persistent viral and bacterial infections have been postulated. The role of HTLV was established in a study from New York on 50 patients which showed the presence of HTLV pol and/or tax proviral sequences in 92% of the patients tested (37). However a study on 50 European patients from Switzerland for HTLV did not seem to play a role in the etiology of CTCL (38). Borrelia burgdorferi-specific sequence was detected in 18% (15 of 83 skin samples) of patients with MF(39). Herne et al reported significant cytomegalovirus (CMV) seropositivity in patients with mycosis fungoides (MF) and Sézary syndrome (SS)(40). The role of HLA-DR5 and HLA-DQB*03 in patients with MF/SS had already proved by the same authors previously (41).

The role of dendritic cells (DC) in proliferation of T cells and formation of Pautrier's microabscesses also has been postulated. This is supported in a study by Jackow CM et al, concluding that cutaneous T cell lymphoma cells proliferate in vitro in response to T cell receptor stimulation by autologous DC, which have previously engulfed and processed antigens from apoptotic autologous cutaneous T cell lymphoma cells (42).

Clinical features: MF has male predominance {M:F-2:1}(43–45) with a median age of presentation at 33-50 years(44,45). The disease is localized to non photoexposed areas including buttocks, trunks and extremities (6). The lesions can also present in groin, breast, chest and occasionally head and neck region (14). In late cases dissemination to lymph node and visceral organ can be seen (6). In literature, different types of MF were reported, the most common being the classical form {36%} followed by the hypopigmented form {35%}. Other described forms are folliculotropic, granulomatous slack skin and pigmented purpura like(6). There are three progressive stages of classical form of MF which are the premycotic or the patch stage, plaque stage and the tumor stage or erythroderma (14,46). MF has an slow progression over years with indolent course with almost 80-90% cases presenting with stage IA and IB (44,45). The most common presentation is the patch stage with a frequency of almost 90% followed by the plaque and the tumor stage (6). The early phase consists of erythematous, flat macules or patches {measuring from 1 to 5 cm in diameter}. As the patches become increasingly infiltrated they evolve into palpable reddish-brown infiltrated plaques with well-marginated borders. The Patch and plaque stage are a continuous form of disease and sometimes differentiation may not be possible. These lesions usually have an asymmetrical distribution, mostly involving the buttocks, lower trunk, groin, axillary region, and breasts(14). In the late stage of MF the patients show features of all three phases or diffuse erythroderma sparing flexural areas (14,46). Usually the tumor nodules are associated with overlying ulceration (46). Majority of the patients presented with skin limited disease only (approximately 85%) (45). Except Sézary syndrome, the bone marrow involvement is rare (46). There is increased risk of secondary malignancy especially Hodgkin's lymphoma (47). A different

staging system for MF and SS proposed by International Society for Cutaneous Lymphomas {ISCL} and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer {EORTC}(19) {Appendix 7}.

Morphology: Histologically, the MF is characterized by epidermotropism by atypical T lymphocytes with hyperchromatic hyper convoluted/cerebriform or pleomorphic nuclei and perinuclear halo (14). The tumor cells vary from size of a small lymphocyte {known as mycosis or small Sézary cell} to approximately twice that size {true mycosis or large Sézary cell} (48). Usually, the histomorphological features and involvement of atypical infiltrates closely correlate with clinical stage.

In the initial patch stage the atypical infiltrate admixed with small T lymphocytes are localized to upper dermis with perivascular, lichenoid or band like infiltrate (14). Single cell exocytosis with epidermotropism is seen but intraepidermal clusters of atypical cells {Pautrier's microabscesses} are rarely present (14). In one of the article published by Smoller et al. Pautrier's microabscesses were defined as at least 4 atypical lymphocytes being present in a single intra epidermal vacuole (49). In a similar study and study done by Massone et al. showed haloed lymphocytes were found in approximately 40-60% of cases (49,50). Massone et al also described basilar lymphocytes as another feature of MF seen in around 23% of cases and was defined as a presence of at least 4 lymphocytes along the basal layer(50). The other features which favor a diagnosis of MF are disproportionate epidermotropism {several lymphocytes in a background of scant spongiosis} and pagetoid epidermotropism (49,50).

In the next plaque stage the atypical lymphoid cell infiltrate is dense and shows a superficial dermal band like infiltrate of atypical lymphoid cells. Pautrier's microabscesses may be found in approximately 25% of cases. Mixed inflammatory infiltrates like histiocytes, eosinophils and plasma cells are present in dermis (43). The deep dermis and subcutis are usually normal (43).

In the tumor phase, the lymphoma cells infiltrate the whole dermis and extend to sub cutis and overlying epidermis with a nodular and/or diffuse growth pattern. In tumor stage, the atypical cells are predominantly medium sized, and epidermotropism can be lost (14,43). In about 50% of the cases few scattered large atypical pleomorphic to anaplastic cells can be found (14,43). Large cell transformation (LCT) has been defined as the presence of large cells {at least 4 times the size of a small lymphocyte} exceeding 25% of the cells of the total lymphoid infiltrate or forming microscopic nodules (51,52). In various studies the frequency of large cell transformation has been reported to be between 2-8%(45,52). In a study done by Diamandidou E et al. the median time between diagnosis and the transformation was approximately 12 months and was seen particularly in the tumor stage (53). A multivariate study done in Netherland on 100 patients has shown that CD30 negativity, folliculotropic MF, extent of skin lesions and extracutaneous transformation were associated with reduced disease-specific survival (DSS) (54). Also in the same study they made observation that that patients with stage IIB with LCT should not be treated more aggressively than patients presenting with stage IIB without LCT, as suggested by recent National Comprehensive Cancer Network guidelines (55).

The sites of transformation may vary; generally the first site of transformation is usually skin as shown in a study done by Barberio E et al. (52). Transformation at other sites such as liver and

lymph node has been reported (53). Regional lymph nodes may show a spectrum of histopathological features ranging from reactive hyperplasia, to dermatopathic lymphadenitis and involvement by lymphoma (43).

Immunophenotype: The atypical lymphoid cells express pan T cell antigens CD2, CD3 and CD5 with aberrant loss of CD7 (43). The typical phenotype is of CD4+ helper T cell phenotype (43). This helper T cell phenotype is retained until the tumor stage of MF or lymph node involvement. In a study done by Nikolaou V et al, less than 5% of the cases have cytotoxic CD8+ phenotype, usually associated with hyperpigmentation and poikiloderma and have an indolent course (56,57). TIA-1 and Granzyme B are expressed rarely and usually associated with a cytotoxic CD8+ phenotype (58). The expression of cytotoxic proteins increases from patch stage to tumor stage (57) . A study done by Kadin ME et al. on 96 patients with early MF from USA has shown that high soluble CD30 (sCD30) was associated with worse survival(59). In large cell transformation, the large cells are usually CD30 positive (52,53).

T-cell rearrangement study: In a study done by Kim et al. shown that T cell receptor rearrangement was present in about 70-85% cases (44,60).

CLINICO-PATHOLOGIC VARIANTS OF MYCOSIS FUNGOIDES:

These include Folliculotropic MF (61,62), Pagetoid reticulosis and Granulomatous Slack skin. The former has a worse prognosis compare to the latter Rather than non photoexposed areas as in MF, the folliculotropic MF involves the head and neck area (61). Hiistologically, folliculotropic MF is characterized by folliculotropism with perifollicular infiltrates of atypical CD4+ T lymphocytes, often with sparing of epidermis and at times epithelial mucin degradation

(61). Follicular mucinosis is almost always seen along with infiltrates of eosinophils and plasma cells (61). Pagetoid reticulosis (Woringer-Kolopp type) is considered as an MF variant because of its clinical, evolutive and anatomopathological characteristics. Histologically, apart from intense epidermotropism of small or medium sized atypical lymphocytes, it shows pronounced epidermal hyperplasia (67). The immunophenotypic pattern is a bit different in pagetoid reticulosis since here atypical cells are positive for both CD4 and CD8 or negative for both, as well as these cells express CD30. The proliferation index estimated by Ki-67 is higher than 30% in pagetoid reticulosis and lower than 10% in MF, but it still has a good prognosis(65). Granulomatous slack skin (69,70) shows a clinical pattern of flaccid, atrophic, pendular and redundant cutaneous lesions in the axilla and groin. Histologically it is characterized by agranulomatous infiltrate with proliferation of atypical clonal CD4+ T cells with abundant macrophages and multinucleate giant cells. Epidermotropism is generally absent or usually subtle. Elastic tissues are usually diminished to absent and phagocytosis of elastic fibers by giant cells and macrophages are a conspicuous feature(71). The prognosis is good without any extracutaneous manifestation (69,71). Occasional rare case reported by Jieliu et al with involvement of lymph nodes, liver and spleen (70).

CLINICAL AND HISTOLOGICAL VARIANTS DESCRIBED IN LITERATURE:

Hypo pigmented mycosis fungoides: It is characterized by isolated or multiple erythematous and hypochromic lesions of small or large diameters, sometimes alopecic (72). Coexistence with other phases of MF may be seen. In this clinical variant of MF children and adolescents are most commonly involved with skin phototype IV-VI(73). A study by Shabrawi-Caelen LE et al and

Ardigo et al showed that patients with hypo pigmented MF had an increased frequency of CD8 positive lymphocyte (72, 73). Differential diagnosis includes pityriasis alba (74). The prognosis is similar to classical MF with good therapeutic response to phototherapy and regaining of pigmentation (75).

Erythrodermic mycosis fungoides :

In a rare event classical MF patient in late stages may show erythroderma. There are almost indistinguishable from SS. The detailed clinical history and definite criteria of SS may helpful to delineate the difference (76). The histological and immunophenotypic aspects are almost similar to those of MF. After treatment, the patient may relapse with conventional stage wise manner or relapse with the previous erythrodermic pattern (76).

Poikilodermatous mycosis fungoides (poikiloderma atrophicans vasculare):

This variant is characterized by erythematous brownish patches, alternating hypo and hyperpigmentation with an atrophic pattern and with xerosis and telangiectasias on the surface (77). In a series by Abbott RA et al, this condition was more common in young patients and associated with Lymphomatoid papulosis (77). Breasts, trunk, gluteal region and flexural regions are the leading sites of involvement. Generalized disease also had been reported (77). Histology characteristically shows atrophic epidermis with lichenoid infiltrate, loss of interpapillary crests and fibrosis of the papillary dermis (77,78).Telangiectasia and melanophages are observed in the superficial dermis (77).The immunohistochemical pattern is predominantly CD8 positive and CD4 negative.The overall prognosis appears favorable with good response to phototherapy (77). If other features of classical MF are not present, the

diagnosis is difficult and is based on clinical progression, histomorphological and immunophenotypic correlation (77,78).

Other rare forms include Purpuric mycosis fungoides, Syringotrpic Mycosis Fungoides and Vesicobullous Mycosis Fungoides**.** In Purpuric MF the patch lesions are persistent and pigmented. Histomorphologically, they show extravasated RBCs in the superficial dermis, melanophages and histiocytes (79). Most cells are CD4 positive, but there may be expression of CD8 positive cells. Monoclonal T cell receptor (TCR) gene rearrangement has been shown in the infiltrate of purpuric MF, but it may also present in cases of purpuric pharmacodermias. Therefore, it is not always easy to clearly define the diagnosis of purpuric MF(79,80). The prognosis is generally good (79). Syringotropic MF contains atypical lymphoid cells around eccrine sweat glands and ducts (81). Clinically, the lesions may be a single erythematous brownish plaque and slightly desquamative, or in groups of erythematous papules (81). There is frequent association with alopecia (82). There is no preferred location. The infiltrate may extend to follicles and overlying epidermis. Epidermotropism and formation of Pautrier's microabscesses are rare (81,82). Clonal TCR rearrangement is seen(81–83). Vesiculo-bullous MFis very rare and presents as single scattered or multiple, flaccid or tense lesions. The patients were generally older and mostly Caucasian (84,85). The trunk and limbs are the preferential locations (85). Histologically, the lesions show epidermotropism and even Pautrier's microabscesses (84,85). The vesicles may be subcorneal, intraepidermal or subepidermal locations; therefore, bullous eruptions could be flaccid or tense. It was postulated in a study by Requena L et al. that the bullous originates from the confluence of Pautrier's microabscesses

and the accumulation of lymphocytes in the basal layer, thus missing the dermal-epidermal cohesion (86).The presence of these lesions in MF indicates bad prognosis (84,85).

Other subtypes: Apart from the subtypes described above, MF may manifest as or be accompanied by atypical morphological expressions, such as papular, anetodermic, hyperkeratotic, vegetative, pustular, ichthyosiform or even "invisible" MF(87,88).

MYCOSIS FUNGOIDES IN CHILDHOOD AND ADOLESCENCE

Overall only 5% of all MF cases occur in childhood and adolescence; however, MF is the most common cause of cutaneous lymphoma at this age range (89). The incidence appears to be increasing, particularly hypochromic subtype in patients with a high skin phototype (89). The incidence particularly in Asians and Indians is high up to 32% reported in a study by Doshi et al (30,90). The second subtype of MF reported in this age group is Woringer-Kolopp pagetoid reticulosis. Few case reports similar to lichenoid and acute varicelliform pityriasis also had been reported, and they are difficult to be diagnosed as MF(91,92). The course and prognosis of MF in this age group is controversial. Some authors suggest aggressive course with extracutaneous manifestation; however few others report that progression is similar to classical MF (68,91).

Variants in India: There were no large studies for MF variants in India. A study done on MF variants by Doshi et al showed that after patch stage of MF, the common variants were hypopigmented {32%}, plaque stage of MF{9%}, poikilodermic {7%} and granulomatous{2%}(30)**.**

Treatment and Prognosis: Available treatment modalities are topical steroid therapy, phototherapy {PUVA}, acitretin, methotrexate, radiation therapy and in few cases systemic

chemotherapy (44,60,93). The 5-year disease specific survival of patients with stage IA, IB and IIA disease was 100%, 96% and 80% respectively and only 40% for patients with stage III disease (91). Large cell transformation runs an aggressive clinical course with median survival of 19.4 months as compared to the untransformed cases which is 163 months (53). According to Talpur R et al the risk factors associated with progression or deaths were advanced age, plaque stage, serum lactate dehydrogenase level, and tumor area (31). In the same study the progression to higher stage occurred in 11.6% patients and 8.1% patients died of the disease. Quaglino P et al in his study showed that blood involvement was the most frequent extracutaneous site of disease progression (94). Patients with stage IA/IB disease showed low annual incidence of disease progression to tumor stage, in contrast to stage IIB disease which had higher risk of progression to higher stage within a year (94).

SEZARY SYNDROME

Sézary Syndrome constitutes 3% of all cutaneous lymphomas, and is characterized by a triad of manifestations: erythrodermia with pruritus, lymphadenopathy and atypical circulating lymphocytes (95). The frequency in different studies in India is 1.5-3% (12,30).

The diagnostic criteria for the syndrome, as recommended by ISCL-EORTC are that the circulating monoclonal lymphocyte population should be identified by molecular or cytogenetic methods and there should be an identity between the circulating T-lymphocyte clone and the clone presented in the skin, in addition to one of the following: at least 1,000 Sézary cells per mm(96) of peripheral blood, an increased population of $CD4^+/CD7^-$ in peripheral blood with remarkable predominance of $CD4^+$ cells in relation to $CD8^+$(CD4/CD8 ratio > 10), Sézary cells

with a diameter > 14 µm representing > 20% of the circulating lymphocytes and, some markers like CD2, CD3 and CD5 must be absent(2)

Clinical features: The patients present with erythroderma associated with exfoliation, edema, lichenification and intense pruritus (6). Alopecia, palmo-planter hyperkeratosis, alopecia, lagophthalmossis and onycodystrophy can be associated (97). The disease affects elderly with equal sex distribution (6,30). It is very difficult to discern erythroderma in SS from those associated with other diseases (98).In the WHO-EORTC classification, MF and SS are listed as different entities, and patients with a previous history of classical MF with all stages, who develop erythroderma are diagnosed as having an erythrodermic form of MF instead of SS(2). Although the syndrome is considered and believed as a leukemic phase of T-cell cutaneous lymphomas, bone marrow involvement is rare, and it is only found in advanced forms of the disease(46)

Morphology: Histomorphologically SS and MF show similar features excepting the fact that in the former the cellular infiltrates are more often monotonous and epidermotropism may sometimes be absent (6). Involved lymph nodes show diffuse effacement of architecture and dense monotonous infiltrates of Sézary cells.

Immunophenotype: Tumor cells express pan T cell antigens CD2, CD3, and CD5 with a helper CD4+ T cell phenotype (2,6). CD8 and CD7 are usually negative (6,99). T cell rearrangement {TCR β} is usually seen (2). Matthew J W et al showed 100% expression of MUM1 in the neoplastic cells in a series of 8 cases as compared to mycosis fungoides wherein it was only 8% (100).

Staging: Similar staging system as used for MF and by definition the SS is classified in stage III from the beginning.

Prognosis: SS has aggressive course and most patients die of opportunistic infections. The mean survival period is 2-4 years (101). Both MF and SS have increased chance of developing malignant neoplasm as well as second lymphoma. Patients with a B cell lymphoma may develop MF or SS more frequently than the general population (68).

SUBCUTANEOUS PANNICULITIS-LIKE T CELL LYMPHOMA

Definition : Subcutaneous panniculitis-like T cell lymphoma {SPTCL} is a cytotoxic T-cell lymphoma, which preferentially infiltrates subcutaneous tissue and is composed of atypical lymphoid cells of varying size, typically with karyorrhexis of tumor cells and associated fat necrosis (2).

Frequency: SPTCL is a cutaneous T cell lymphoma amounting to less than 2% of all peripheral T cell lymphomas and approximately 10-15% of all primary cutaneous lymphomas in various studies (9,102–104). However, in western literature the frequency is 1% (6) and it is around 11% and 15% in Korean(10,105)and Indian study(12) respectively.

Clinical features: The median age group in different studies is 25-40 years(106–108) with a slight female predominance(106,108,109). Most common sites of involvement in descending order are the legs, arms, trunk and face (106,108,110). In almost all cases the presenting skin lesions are nodules and plaques (106). Generally the nodular lesions or deeply located plaques(106). This disease commonly has multifocal lesions (106). Common associated finding

is generally hemophagocytic syndrome (106,107,111) which can be florid sometimes(111). Often marrow is not involved, but shows hemophagocytosis or increase in reticuloendothelial cell activity (106,112,113). Organomegaly and lymphadenopathy can be seen sometimes (106,112).

Morphology: The infiltrate is predominantly a lobular panniculitis. Mild to moderate extension into deep dermis and surrounding skin adnexae is often described (106,108,110). Very rarely this infiltrate may extend to superficial dermis and epidermis (106,109). Angiodestruction, angioinvasion and Angiocentricity are seen commonly (108,110,112–114). Important feature to differentiate from benign panniculitis is that the connective tissue septae are infiltrated by neoplastic cells here (114). The neoplastic T cells are of small to medium sized with irregular and often hyperchromatic nuclei. Rimming of individual adipocytes is a characteristic feature (106,109). Fat necrosis and karyorrhexis are almost always present (106,108,109). Few reactive lymphocytes and foamy histiocytes are almost always admixed with these atypical cells (106,114). Very rarely granulomas are present with multinucleated giant cells is seen (108,111). Erythrophagocytosis is also often present in other extracutaneous organs like marrow, liver and spleen (111). The pertinent histologic features of SPTCL as described in the WHO classification include neoplastic T cells with preferential involvement of the subcutaneous tissue and relative sparing of overlying epidermis and dermis, rimming of neoplastic cells surrounding individual fat cells and clonal TCR gene rearrangement.

Immunophenotype: The neoplastic cells express CD3, CD8 with expression of cytotoxic granule associated proteins {granzyme B, TIA1 and perforin}(56,106,108,112,114). CD4 is usually

negative or very rarely expressed (112). There is an aberrant loss of other pan T cell antigens CD7, CD5 and CD2 (106). CD56 is usually negative (106,108). EBV LMP1 and EBER are negative (106,109,114). T cell rearrangement is seen in almost all cases (106).

Treatment and prognosis: Systemic multiagent chemotherapy is used. Patients without hemophagocytosis have a significantly better 5-year overall survival {91%} than patients with it {46%} (106). Angioinvasion is associated with adverse prognosis with increased mortality (108).

PRIMARY CUTANEOUS CD30^{+} LYMPHOPROLIFERATIVE DISORDERS

History of CD30 lymphoproliferative disorder: In 1968, "Lymphomatoid papulosis" was described by Macaulay as a benign clinical form of CTCL that develops in outbreaks, despite its malignant morphological aspect on histopathological examination (115,116).

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA

Primary cutaneous anaplastic large cell lymphoma {cut ALCL} is a lymphoma composed of large cells with an anaplastic, pleomorphic or immunoblastic morphology that express the CD30 antigen in>75%} of the tumor cells(6,117). Cutaneous ALCL and Lymphomatoid papulosis (LyP) together come under the category of primary cutaneous CD30 positive lymphoproliferative disorders.

Frequency: Cutaneous CD30 positive lymphoproliferative disorder is a rare subtype accounting for 1-5% of all cutaneous lymphomas and 20-30% of peripheral T cell lymphomas (3,4,28,103,104,118). (6) Primary cutaneous ALCL constituted 8% in western study (6) and 2-3% in previous Indian studies (12,30).

Clinical features: The median age of diagnosis is 53-60 years (6,117,119). It is male predominant with a male to female ratio of approximately 1.5-3:1(117,119). Most common affected sites are extremities, trunk and face (119). The lesions are usually solitary nodules or papules with a tendency to partial or complete spontaneous regression (117,119). Most of the time the lesions are limited to particular sites, but sometimes it may be generalized (117). Involvement of the regional lymph nodes as a part of extracutaneous dissemination occurs in y 10% of the patients (6,120). Rarely lung, CNS, bone, liver and spleen are also involved (120). Bone marrow is usually never involved (120).

Morphology: There is a diffuse, non epidermotropic infiltrate with cohesive sheets of large anaplastic or pleomorphic cells with abundant cytoplasm and round to oval irregularly shaped nuclei with prominent eosinophilic nucleoli(6). Epidermotropism and angiodestruction can be seen sometimes (119).

Immunophenotype: The neoplastic cells show an activated CD4 positive phenotype with variable loss of CD2, CD5, CD3, and a frequent expression of cytotoxic granule associated proteins {Granzyme B, TIA-1 and perforin} (121,122). CD30 is positive in >75% of the neoplastic cells (123). CD15 and ALK are negative. Hinshaw M et al reported 3 pediatric cutaneous ALCL which bore t {2;5} translocation which had a favorable outcome(124). Expression of MUM1 ranged from 20% to 100% in 2 different studies (100,125).

Molecular genetics: Cut ALCL shows monoclonal T cell expansion and TCR γ gene rearrangement.

Treatment and prognosis: Different treatment modalities are available like radiotherapy, surgical excision, PUVA, topical steroids and multiagent chemotherapy (117). Almost 99% patients achieve complete remission after the initial therapy (117). The five year disease specific survival in cases with skin limited disease and with extracutaneous spread is approximately 90% and 50% respectively (120).

LYMPHOMATOID PAPULOSIS (LyP)

Lymphomatoid papulosis is a chronic, recurrent, self-healing skin disease composed of large atypical anaplastic, immunoblastic or Hodgkin-like cells in an inflammatory background" (2).

Frequency: The frequency of LyP is 12% in western literature (6) and is 17% in a previous Indian study(30).

Clinical features: The disease has slight male predominance with a median age range of 45 years, but may occur in children as young as 4 years (117). Trunk and extremities are the most frequent sites of involvement (6,117). Generalized papules are the most common clinical manifestation (117). Nodular lesions and papulo-necrotic lesions may be present in different stages of development, predominantly on the trunks and limbs (6).

Morphology: Three histological subtypes have been described (116,117). Sometimes there is a combination of any of the three subtypes.

1. Type A, or histiocytic type – Most common type; 82-87% of the cases (116,117). There is a dense wedge shaped mixed infiltrate of large atypical lymphocytes admixed with neutrophils, eosinophils, histiocytes, and small lymphocytes. The large atypical cells are usually scattered or

form small clusters but not sheets ad do not constitute more than 50% of the infiltrate. Rarely there may be adnexotropism (116). Epidermotropism is seen in up to 50% of cases (116).

2. Type B or lymphocytic type – This subtype resembles MF. There is a band like and epidermotropic infiltrate of small to medium-sized lymphocytes with cerebriform nuclei (6). Some cases may show extension into reticular dermis. This has also been referred to in the literature as the MF-like variant.

3. Type C – Similar to type A, but the atypical lymphoid cells either formed sheets or large nodules or represented more than 50% of the infiltrate, simulating ALCL. Admixed inflammatory cells are scanty or minimal. This type is considered as a borderline LyP-ALCL.

Recent new categories- Type D and Type E have been proposed. Both have clinical features of LyP, but the histopathological features resemble primary cutaneous aggressive CD8 positive cytotoxic T cell lymphoma in the former and with angioinvasion (126) in the latter(127,128).

Immunophenotype: The large atypical cells are CD30+(116). The atypical cells show almost similar immunophenotyping as in MF which are CD3+, CD4+, CD8- and CD30- phenotype(6). The expression of MUM1 ranged from 87% to 100% in 2 different studies (100,125).

Molecular genetics: LyP shows monoclonal T cell expansion and TCR γ gene rearrangement (129).

Treatment and prognosis: Almost all cases show spontaneous remission (117). About 60% of the patients do not require any treatment or treatment with topical steroids alone is

satisfactory (117). The prognosis is excellent with almost 100% 10 year disease free survival (117).

ADULT T-CELL LEUKEMIA/LYMPHOMA

Definition - Adult T-cell leukemia/lymphoma (ATLL) is a T-cell neoplasm etiologically associated with the human T-cell leukemia virus 1 (HTLV-1). The cutaneous manifestation is generally a part of widely disseminated disease. However, few cases with slowly progressive course involving only skin has been described (smoldering variant)(130). There are no large studies from India except few case reports and small study including two or three patients (131–133).

Clinical features. The disease is endemic in areas with a high prevalence of HTLV-1 in the population, such as Southwest Japan, the Caribbean islands, South America, and parts of Central Africa. In 1% to 5% of seropositive individuals ATLL may present after more than 2 decades of viral persistence. Characteristically the patients with ATLL show presence of leukemia, lymphadenopathy, organomegaly, hypercalcemia, and in about 50% skin lesions, most commonly in form of nodules or tumors (33%), generalized papules (22%), or plaques (19%)(134). The clinical presentation is similar in Indian as well (133). There are chronic and smoldering variants of ATLL that are frequently present with skin lesions, which may closely resemble MF, whereas circulating neoplastic T cells are few or absent.

Histopathology: Skin lesions show a dermal diffuse infiltration of medium-sized to large T cells with pleomorphic or polylobated nuclei, which often display marked epidermotropism. The histologic picture may be indistinguishable from MF. Few atypical cells with sparse superficial

dermal infiltrates may be present in chronic or smoldering type. The atypical T cells are CD3 & CD4 positive and are negative for CD8. CD25 is highly expressed (130,131,134).

Genetic features*:* There is clonal rearrangement of T-cell receptor genes. Clonally integrated HTLV-1 genes are found in all cases including chronic and smoldering variants, and in doubtful cases this can be useful in differentiating between these variants of ATLL and classical MF or SS (135).

Prognosis and predictive factors: The main prognostic factor is clinical subtype. In acute and lymphomatous variants the survival ranges from 2 weeks to more than 1 year. Chronic and smoldering variants have a more indolent clinical course and a longer survival, but transformation into an acute phase with an aggressive course may occur(130,134).

Treatment: Systemic chemotherapy is required in most cases (136,137). In skin limited variants (chronic and smoldering) targeted skin therapies as in MF may be used.

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

Definition: Extra nodal NK/T-cell lymphoma, nasal type, is a nearly always EBV positive lymphoma of small, medium or large cells usually with an NK-cell, or more rarely a cytotoxic T-cell, phenotype. After the nasal cavity the skin is the second most common site of involvement where skin involvement may be a primary or secondary (138). Distinction between primary and secondary cutaneous involvement is not required, since both groups show an aggressive clinical behavior and require the same type of treatment (139–142,(143).

Clinical features*:* The disease predominantly occurs in adult males and is more common in Asia, Central America, and South America (144). The incidence in India is 0.7% (30). The disease localized to skin generally presents with multiple plaques or tumors preferentially on the trunk and extremities (139–142). Systemic manifestations like fever, malaise, and weight loss may be present and in some cases are accompanied by hemophagocytic syndrome (138). The disease is closely related to aggressive NK-cell leukemia, which also may have cutaneous manifestations, and is also EBV associated (58).

Histopathology: The histomorphology shows dense infiltrates involving the dermis and often the subcutis. Epidermotropism may be present. Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis (144).The atypical cells inNK/T-cell lymphoma may be small, medium to large sized, with most cases consisting of medium sized cells. The cells may have irregular or oval nuclei, moderately dense chromatin, and pale cytoplasm. In some cases a mixed dense inflammatory infiltrate of small lymphocytes, histiocytes, plasma cells and eosinophils can be seen (138).

Immunophenotype: The neoplastic cells express CD2, CD56, cytoplasmic CD3є{epsilon], and cytotoxic proteins (TIA-1, granzyme B, perforin), but lack surface CD3(145). If CD56 is negative, then EBERNA positivity and expression of cytotoxic proteins are required for diagnosis. Latent membrane protein-1 (LMP-1) is inconsistently expressed.

Genetic feature: The T-cell receptor can be rearranged in rare tumors with a cytotoxic T-cell phenotype. EBV is expressed almost in all cases, suggesting a pathogenetic role of this

virus(144). There were not many studies in India which included T cell receptor rearrangement study for diagnostic purpose.

Prognosis and predictive factor: This lymphoma is a highly aggressive tumor with a median survival of less than 12 months (138). Extracutaneous involvement at the time of presentation is the most important predicting factor with poor outcome (138). Patients with only skin lesions showed a median survival of 27 months and with extracutaneous manifestations the median survival was 5 months (138). CD30 and CD56 positive cases have a better prognosis (146).

Therapy*:* Systemic chemotherapy is the first choice of treatment, but the results are disappointing (138).

Variant: Hydroavacciniforme like cutaneous T cell lymphoma is a rare type of EBV associated lymphoma of CD8 positive cytotoxic T cells, which affects children almost exclusively in Latin America and Asia(147–149).Patients present with a papulo-vesicular eruption clinically resembling hydroavacciniforme, particularly on the face and upper extremities (sun exposed areas). The prognosis is poor. In India a case report from CMC, Vellore with similar clinical features was published in a 14 year old boy(150).

PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED

In the WHO classification, Primary cutaneous peripheral T cell lymphoma-unspecified (PCPTCL) represent a group of heterogeneous lymphomas which includes all T cell lymphomas that do not fit into any of the better defined above mentioned subtypes of T cell lymphoma/leukemia. This group includes primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell

lymphoma, cutaneous gamma-delta T-cell lymphoma and primary cutaneous small/medium CD4 positive T-cell lymphoma. For the remaining diseases that do not fit into either of these entities the designation PCTCL, unspecified, is maintained. Before making this diagnosis, Mycosis fungoides must be ruled out by thorough accurate history and clinical examination (143).

History of PTCL unspecified: In 1885, Vidal and Brocq introduced the term "mycosis fungoides d'*emblée*" for cases with cutaneous lymphomatous tumorations (19) without precursor lesions. Currently, this clinical “MF” subtype corresponds to the "unspecific peripheral cutaneous T-cell lymphoma" (19).

PRIMARY CUTANEOUS AGGRESSIVE EPIDERMOTROPIC CD8 POSITIVE CYTOTOXIC T-CELL LYMPHOMA

Definition: This lymphoma is characterized by a proliferation of epidermotropic $CD8^+$ cytotoxic T cells and an aggressive clinical behavior (151,152). Few other T cell lymphomas may express a CD8 positive cytotoxic T-cell phenotype like in more than 50% of patients with pagetoid reticulosis and in rare cases of Mycosis fungoides and CD30 positive lymphoproliferative disorders, in which diagnosis is based on the clinical presentation and clinical behavior (151).

Age and Sex Ratio: In a study done by Berti et al, there was a male predominance with age ranges from 8-91 years {median 53 year}(151). The incidence was <1% in a study by Willemze (6).There was no comparable larger Indian study.

Clinical features: Generally the patients present with localized or generalized hyperkeratotic patch, plaque, multiple eruptive papules, nodules or tumors displaying central ulceration and

necrosis (139,151). These features are very similar to patients with cutaneous gamma/delta T cell lymphoma and generalized pagetoid reticulosis (Ketron-Goodman type)(141). Dissemination to other visceral sites like lung, testis, central nervous system and oral mucosa are common, however lymph nodes are often not involved (151).

Histopathology: The epidermis appears either acanthotic or atrophic with necrotic keratinocytes, overlying ulceration, variable spongiosis, sometimes with blister formation (139,151).There is pronounced epidermotropism with either linear distribution or a pagetoid pattern throughout the epidermis (151). The tumor cells are small to medium or medium to large sized with blastic nuclei. Infiltration and destruction of adnexal structures are commonly seen. There may be angiocentricity and angioinvasion (151).

Immunophenotype: The tumor cells are positive for betaF1, CD3, CD8, granzyme-B, perforin, TIA-1, CD45RA, CD7(+/-) and negative for CD45RO, CD2, CD4 and CD5(139,141,151). EBV latency protein is generally negative.

Genetic features: The atypical lymphoid cells show clonal TCR gene rearrangement (151).

Prognosis and predictive factors: The behavior of these lymphomas is aggressive with a median survival of 32 months (151). The morphology of atypical lymphoid cells does not make any difference in survival (153).

Therapy: The preferred therapy for these lymphomas is doxorubicin based multiagent chemotherapy (56).

PRIMARY CUTANEOUS GAMMA/DELTA T-CELL LYMPHOMA (CGD-TCL)

Definition: CGD-TCL is a lymphoma composed of a clonal proliferation of mature and activated γ/δ T cells with a cytotoxic phenotype. This lymphoma includes cases previously known as SPTCL with a γ/δ phenotype. A related condition may present primarily in mucosal sites(154). Whether cutaneous and mucosal γ/δ TCL are all part of a single disease is not yet clear(145). Since both groups have similar grave prognosis, distinction between 'primary' and 'secondary' cutaneous cases is not useful.

Clinical features: Generally patients present with disseminated plaques or/and ulceronecrotic nodules or tumors particularly on the extremities (155–158). Extra nodal site and mucosal involvement are frequently observed (154),but involvement of other lymphoreticular organs (lymph nodes, spleen or bone marrow) are uncommon(158). In case of panniculitis like tumor, a hemophagocytic syndrome may occur (154,158).

Histopathology: There are three major histologic patterns of involvement in the skin: epidermotropic, dermal and subcutaneous. More often a mixed histologic pattern is present in the same patient155,158). The atypical lymphoid cells are generally medium to large in size with coarsely clumped chromatin. Large cells with blastic morphology (vesicular nuclei, prominent nucleoli) are infrequent. Angioinvasion is common, often with apoptosis and necrosis (110). Similar to SPTCL, the subcutaneous cases may show rimming of adipocytes.

Immunophenotype: Characteristically the tumor cells show a CD3, CD2, CD7 (+/-), CD56 positive phenotype with strong expression of cytotoxic proteins. These cells are negative for

betaF1 and CD5. Most cases lack both CD4 and CD8 though rarely CD8 may be positive (156,158). The neoplastic cells are strongly positive for TCR-delta on frozen sections. The absence of betaF1 may be used to categorize lymphoma as gamma/delta subtype under appropriate circumstances when paraffin blocks are available (156–158).

Genetic features: These neoplastic cells show clonal rearrangement of the TCR gamma gene. T cell rearrangement studies for beta gene may show deletion. EBV is generally negative (154,158).

Prognosis and predictive factors: The disease runs an aggressive course and is generally resistant to multiagent chemotherapy or/and radiation. Median survival is around 15 months(141). There is decreased survival for patients who had subcutaneous adipocytes involved compared to those patients who had epidermal/dermal disease only.

Therapy: Systemic chemotherapy is the preferred mode of treatment, but the results are often disappointing (158).

PRIMARY CUTANEOUS CD4^{+} SMALL/MEDIUM-SIZED PLEOMORPHIC T-CELL LYMPHOMA

Definition: Primary cutaneous CD4 positive small/medium-sized pleomorphic T-cell lymphoma is defined by a predominance of small to medium sized CD4 positive pleomorphic T cells without history of patches and plaques typical of mycosis fungoides with a favorable clinical course (101). The cases in which the cells are positive for CD3, CD8 and negative for CD4 are usually found to have a more aggressive course and these are included in the group of aggressive epidermotropic CD8 positive cutaneous T cell lymphomas (153).

Age and Sex ratio: In a study done by Bekkenk et al, there was a female preponderance with a median age of 69 years (153). There were no large Indian studies for comparison.

Clinical features: These lymphomas characteristically present with a single plaque or tumor, generally on the face, the neck, or the upper trunk (159,160).

Histologic features: These lymphomas show dense dermal diffuse or nodular infiltrates with a tendency to infiltrate the subcutis. Focal epidermotropism may be present. There is a predominance of small to medium sized pleomorphic T cells. Angiocentricity with angiodestruction and epidermotropism may be present (153). A small proportion (<30%) of large pleomorphic cells may be present (160). Few cases show admixture of small reactive lymphocytes and histiocytes.

Immunophenotype: By definition, these lymphomas are CD3 & CD4 positive and CD8 & CD30 negative with loss of pan T cell markers sometimes. Generally cytotoxic proteins are not expressed (153).

Genetic features: There is clonal rearrangement of TCR gene (159,160). Consistent cytogenetic abnormalities have not been identified so far. Demonstration of an aberrant T cell phenotype and clonality are useful to differentiate these lymphomas from pseudo T cell lymphomas, which may present with similar clinical features (161).

Prognosis and predictive factors: These lymphomas have a favorable prognosis with a five year survival of 60-80%(159,160). Cases presenting with solitary/localized skin lesions seem to have an excellent prognosis (153).

Therapy: For patients with localized skin lesions, surgical excision or radiotherapy is the preferred mode of treatment. In case of more generalized skin diseases, cyclophosphamide as single agent therapy and IF-α have been reported to be effective (160). However, the definite therapeutic guidelines for these lymphomas are yet to be defined.

PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED

Definition: This designation is maintained for cutaneous T-cell lymphomas that do not fit into any of the better defined subtypes of cutaneous T cell lymphomas. Hence, always all other T cell lymphomas (three entities mentioned above) must be excluded. The incidence in published western literature is 2%(6). There were no large studies from India to determine the frequency of this entity.

Clinical features: Generally this affects adults who present with solitary localized or generalized nodules or tumors (153). There was slight male preponderance in one morphology based study which included 82 patients (153).

Histopathology: The lesions show non epidermotropic nodular or diffuse infiltrates with variable numbers of medium to large sized pleomorphic or immunoblast like T cells. Large atypical lymphoid cells represent at least 30% of the tumor cell population (162).

Immunophenotype: Most of the patients show an aberrant CD4 positive T cell phenotype with variable loss of pan T cell antigens. CD30 staining is negative or restricted to a few scattered tumor cells. Co-expression of CD56 and cytotoxic proteins expression may be seen in rare cases (153).

Prognosis and predictive factors: The prognosis of this lymphoma is generally poor with five year survival rates of <20% (15,101,153,162). There is no statistical difference in survival between cases with solitary/localized or generalized skin lesions (153).

Treatment: Multiagent chemotherapy is the preferred mode of therapy.

PRECURSOR HEMATOLOGIC NEOPLASM

$CD4^+/CD56^+$ HEMATODERMIC NEOPLASM

Definition: In the WHO classification, this lymphoma is included as a clinically aggressive neoplasm with a high incidence of cutaneous involvement and risk of leukemic dissemination. The morphology and CD56 expression initially suggested an NK-precursor origin (2). More recent studies suggest derivation from a plasmacytoid dendritic cell precursor (163,164, 165).
Frequency: The frequency of this lymphoma Is 0.7% (166). The males were twice in number (2:1) with a median age of 65.3 years (166). There are no large studies in India, except a case report in which lower age {27 years} was documented (167)

Clinical features: This lymphoma commonly presents in the skin with solitary or multiple nodules or tumors with or without extracutaneous manifestations (168). Nodal and bone marrow involvement are present in half of the patients (138,163). This lymphoma should be differentiated from myelomonocytic leukemia cutis and from so-called 'aleukemic leukemia cutis'(141).

Histopathology: These lymphomas show diffuse dermal monotonous infiltrates of mitotically active medium sized cells with finely dispersed chromatin, absent or indistinct nucleoli and scant cytoplasm resembling lymphoblasts or myeloblasts and almost sparing the epidermis (163,165,167,168).Inflammatory cells are absent. Necrosis or angioinvasion is not present.

Immunophenotype: The tumor cells are positive for CD4, CD56, CD7 (+/-), CD2(-/+), CD45RA and negative for CD8, surface/cytoplasmic CD3 and cytotoxic proteins(2,163). TdT and CD68 may be positive. Stains for CD3 and myeloperoxidase should always be performed in order to exclude lymphoblastic and myeloblastic neoplasms (2). The cells are also positive for CD123 and TCL1, both of which support origin from plasmacytoid dendritic cells (164,169).

Genetic feature: TCR genes are in germline configuration. The neoplastic cells do not express EBV.

Prognosis and predictive factors: This neoplasm is aggressive with a median survival of 14 months (163,165,168).

Treatment: Complete remission can be achieved with systemic chemotherapy, but early relapse unresponsive to further chemotherapy is the rule. There is no significant difference in survival between patients presenting with skin lesions with or without associated extracutaneous disease (138).

CUTANEOUS B CELL LYMPHOMAS

This group of lymphomas was the most controversial and debatable during consensus meet at Zurich (6). Finally after discussion, three entities were included; namely Primary cutaneous marginal zone B cell lymphoma, Primary cutaneous follicle center lymphoma {PCFCL} and

Primary cutaneous diffuse large B cell lymphoma, leg type {PCDLBCL-leg} the last with an aggressive course and poor outcome (16). Immunophenotyping and molecular studies are also distinct for these lymphomas especially PCFCL (6) compared to their nodal counterpart. There are also other provisional categories, the lymphomas not fitting into either of the above categories with large cell morphology {PCDLBCL-other} and Primary intravascular large B cell lymphoma.

Frequency: The reported frequency was higher in western studies {23-26} which showed a frequency of 25% similar to that mentioned in WHO(6,8). In India the frequency was 5.6% (30) almost similar to a Korean study{4%}(105).

PRIMARY CUTANEOUS MARGINAL ZONE B CELL LYMPHOMA

Definition: Primary cutaneous marginal B cell lymphoma (PCMZL) is an indolent lymphoma composed of small B cells, including centrocyte like (marginal zone) cells, lymphoplasmacytoid cells and plasma cells. Previously this tumor was tagged as primary cutaneous immunocytoma (170).

Frequency: The study done by Senff {300 cases} and Willemze {317 cases} showed the frequency of this lymphoma to be 23% and 7% respectively (6,16). There were no major studies in India, those sub classify cutaneous B cell lymphomas into different cadres.

Age and Sex ratio: This lymphoma is common in the fourth to fifth decade with male preponderance (16,171). There have been case reports and a small study from India with similar age group and sex ratio (30,172).

Clinical features: Most patients with this lymphoma present with red to violaceous papules, plaques or nodules localized preferentially to the trunk or extremities (especially the arms)(6). In a minority of the European cases, association of this lymphoma with Borrelia burgdorferi infection has been reported, but not in Asian or US cases(173–176). Nodal involvement is rare (16), however a case report from India showed that lymph node involvement can be seen with morphology resembling Lennert'slymphoma(172).

Histopathology: PCMZLs show nodular to diffuse dermal infiltrates with sparing of the epidermis. The infiltrates are composed of small lymphocytes including marginal zone B cells (centrocyte-like cells), lymphoplasmacytoid cells, and plasma cells admixed with small numbers of centroblast or immunoblast like cells and many reactive T cells. They may be surrounded by a population of small to medium sized cells with irregular nuclei, inconspicuous nucleoli and abundant pale cytoplasm (marginal zone B cells)(177,178).

Immunophenotype: The atypical cells in PCMZL express CD20, CD79a, and bcl-2, but are negative for CD5, CD10, and bcl-6 which may be useful in distinction from primary cutaneous follicle center lymphoma (179).

Genetic features: There is clonal rearrangement of immunoglobulin heavy chain (IgH) genes(180). Study done by Streubel B et al suggested the presence of the balanced translocation between the IGH gene on chromosome 14 and the MLT gene on chromosome 18 and translocation involving IGH gene and FOXP1 gene on chromosome 3 in a proportion of primary cutaneous marginal zone lymphomas(180).

Prognosis and predictive factors: The prognosis of this lymphoma is excellent with a 5 year survival close to 100%(173,177,178).

Therapy: Radiotherapy or surgical excision is preferred for patients with a solitary or a few lesions. Systemic antibiotics should be tried first in patients with B. burgdorferi infection(181) In approximately 50% of patients presenting with multifocal lesions, chlorambucil or intralesional/subcutaneous administration of interferon alpha may produce complete responses(181). A study done by Soda R et al shown very good response with the use of systemic or intralesional use of anti-CD20 antibody(182).

PRIMARY CUTANEOUS FOLLICLE-CENTER LYMPHOMA

Definition: Primary cutaneous follicle center lymphoma (PCFCL) is defined as a tumor of neoplastic follicle center cells with a follicular, follicular and diffuse or a diffuse growth pattern composed of a mixture of small and large cleaved follicle center cells (centrocytes) and variable numbers of large noncleaved follicle center cells with prominent nucleoli (centroblasts), which generally present on the head or trunk(6).

Frequency: This lymphoma constitutes 11% and 50% of all cutaneous lymphomas and primary cutaneous B cell lymphomas, respectively, in western literature(6,16) and as low as 1% in far east study(105). There were no large Indian studies to document the relative frequency.

Age and Sex ratio: Common in fifth to sixth decade with a male preponderance(16). There were no Indian studies to document demographic and epidemiological data.

Clinical features: This lymphoma has a characteristic clinical presentation with single scattered or grouped plaques and tumors, preferentially located on the scalp or forehead or on the trunk(183,184).

Histopathology: PCFCLs show nodular to diffuse dermal infiltrates with almost constant sparing of the epidermis(6). Early and small lesions contain a mixture of centrocytes, few centroblasts

with a background of many reactive T cells. Multi or polylobated centrocytes are a common feature of this lymphoma. The follicles are not well defined with absent tingible body macrophages and generally have a reduced or absent mantle zone(185,186). With progression to higher (tumorous) lesions these atypical B cells increase both in number and size, whereas the number of reactive T cells steadily decreases(184).

Immunophenotype: The atypical cells are positive for CD20 and CD79a and may show monotypic staining for surface immunoglobulins (sIgs)(6). However, absence of sIg is common in higher lesions showing a diffuse population of large follicle center cells. This lymphomas consistently express bcl-6 as shown in a study done by De LevalLMD(179). Unlike nodal and secondary cutaneous follicular lymphomas counterparts, this lymphoma does not express bcl-2 protein or show faint bcl-2 staining in a minority of atypical B cells(187,188).

Genetic features: Immunoglobulin genes are clonally rearranged. In support of follicle center cell origin somatic hypermutation of variable heavy and light chain genes has been demonstrated(189,190). In contrast to systemic follicular lymphomas and few DLBCL cases, this lymphoma does not show the t(14;18) as mentioned in different studies(186,188,191,192).

Prognosis and predictive factors : Regardless of the growth pattern, the number of blast cells or the presence of either localized or extracutaneous skin disease, these lymphomas have an excellent prognosis with a five year survival of more than 95%(101,183–185,193). A study by Grange F et al. suggested that strong expression of bcl-2 with a diffuse large cell histology is associated with a more unfavorable prognosis(194).

Therapy: Radiotherapy is the preferred mode of therapy in patients with localized or few scattered skin lesions, even in cases with a predominance of large cleaved cells(193,195,196). A

study by Paul T et al showed beneficial effects of systemic or intra lesional administration of anti-CD20 antibody (rituximab) therapy in a small series of primary cutaneous follicle center lymphomas, but the long-term effects of this therapy have yet to be determined(197).

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

Definition: Primary cutaneous diffuse large B cell lymphoma, leg type(PCDLBCL-leg type) is a distinct subtype of PCLBCL with a predominance of confluent sheets of centroblasts and immunoblasts characteristically presenting with skin lesions on the legs(6). Very rarely the skin lesions with similar morphology and phenotype may arise at sites other than legs(6).

Frequency: This lymphoma constitute 19% and 4% in a study done by Senff and Willemze respectively(6,16). There were no large Indian studies to document the frequency of this lymphoma.

Age and Sex ratio: Common in fifth and sixth decade with female preponderance(6,16). A study from India included two younger patients {27 and 38 years} with equal sex ratio(198).

Clinical features: This lymphoma predominantly affects elderly patients and in particular, female(194,199). Generally the presentation of patients with this lymphoma is the occurrence of rapidly growing red or bluish-red lesions on one or both legs. The nomenclature is a misnomer as it can be found anywhere with similar morphology and immunophenotype, as documented in a case report from India which included a case of PCDLBCL-leg type on both upper arms(200). In contrast to other primary cutaneous B cell lymphomas, PCBCL-leg type is an aggressive neoplasm with adverse prognosis and more often metastasis to extracutaneous sites(193,199).

Histopathology: This lymphoma shows diffuse dermal infiltrates of monotonous populations or confluent sheets of centroblasts or/and immunoblasts which many times extend to subcutis(193,199). Frequent mitotic figures are present. Few reactive T lymphocytes may be present in the perivascular region(6).

Immunophenotype: The neoplastic B cells are positive for monotypic sIg and/or cIg and CD20 and CD79a. In contrast to primary cutaneous follicle center lymphoma, this lymphoma shows strong bcl-2 expression, even in cases not localized to the legs(188,194,201). CD10 is generally absent, whereas Bcl-6 is expressed by most cases(201). Most of these lymphomas express MUM-1/IRF4 protein(202) .

Genetic features: A study done by Geelen FA et al. showed that t(14;18) was not found in PCLBCLs, although strong bcl-2 expression was common(188). Study on tumor suppressor genes by Child FJ et al shown inactivation of p15 and p16 by promotorhypermethylation in 11% and 44% of primary cutaneous diffuse B cell lymphoma respectively(203). In up to 85% of cases chromosomal imbalances have been identified, with gains in 18q and 7p and loss of 6q as the most common findings(204,205).

Prognosis and predictive features: The five year survival of 78 cases included in the Dutch and Austrian registries was 55%(6). A multicenter study done by Grange F et al shown that PCLBCLs on the leg had an inferior prognosis compared to PCLBCLs presenting at other sites(206).

Therapy: The patients with this lymphoma should be treated as systemic DLBCLs with anthracycline based chemotherapy(199,206). Radiotherapy may be useful in patients presenting with single small tumor localized to skin(206). As mentioned in a study by Heinzerling LM some patients showed benefits with systemic administration of anti-CD20

antibody (rituximab), lack of long term follow up data makes the therapy with this agent debatable(207). A young patient in India treated with R-CHOP and field radiotherapy. During follow up for two years this patient found to be asymptomatic(198).

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, OTHER

The term primary cutaneous diffuse large B cell lymphoma, other(PCDLBCL-other), refers to cases of large B cell lymphomas arising in the skin which do not fit into above mentioned category of PLCBCL-leg type or the group of PCFCL(6). These rare cases included morphological variants of DLBCL, like anaplastic or plasmablastic type(208) or T-cell/histiocyte rich large B cell lymphoma(209). Commonly these cases are skin manifestation of a systemic lymphoma. As mentioned in a study done by Nicol I et al. plasmablastic lymphomas are almost exclusively seen in the background of HIV seropositivity or other immune deficiencies(208). Clinically these lymphomas are difficult to differentiate from PCFCL and PCMZL(6). In contrast to the nodal counterparts, they appear to have an excellent prognosis(209). In addition to the above mentioned cases, rare cases of primary cutaneous intravascular large B cell lymphoma may be included in this category(210). There were no Indian studies to document this subtype.

Intravascular large B cell lymphoma (IVLBCL) is a well-defined subtype of LBCL, defined by an accumulation of large neoplastic B cells within blood vessels commonly affecting males in sixth and seventh decade(210). In a study done by Perniciaro C et al. these lymphomas preferentially affected the central nervous system, lungs, and skin and were generally associated with a poor prognosis(210). There are two subtypes: Western {with cutaneous and neurological complications} and Asian {multi organ involvement with hemophagocytic syndrome}(211). The

former one is associated with a good prognosis(211). The proposed mechanism is defective Beta 1 integrin and CD11a results in ineffective diapedesis(212)..

A study done on 38 patients by Ferreri AJM et al showed that patients with only skin lesions appeared to have a significantly better survival than patients with other clinical presentations (3 year overall survival was 56% versus 22%)(213).

ROLE OF NOTCH-1 AND FOXP1 IN PCTCL AND PCBCL:

Notch is a member of the four transmembrane receptor family (Notch1 to 4), which is driven by direct cell contact with ligands of the Jagged/Delta family. Notch signaling is considered to be indispensable in normal T cell development(214). As these pathways are very crucial in the control of proliferation/ differentiation and apoptosis, deregulation of Notch pathway may result in cancer. KamstrupMR et al. showed increased expression of Notch signaling (especially Notch1) in primary cutaneous CD30 positive lymphoproliferative disorders (including anaplastic large cell lymphoma and Lymphomatoid papulosis) (215). A study done on 40 biopsies of MF and SS by Maria et al showed that Notch was expressed in a stage dependent manner in MF and in SS(216). In the same study, they showed Notch inhibition by anti- enzymatic mechanisms can induce apoptosis in T cell lymphoma cell lines, paralleled by the inhibition of the survival pathway regulated by nuclear factor-κB and FOXO3a(216).

FOXP1 is a protein expressed in activated B cells and overexpressed in few subtypes of DLBCL, including primary cutaneous large B cell lymphomas, leg type as published in a study by Kodama K et al. (217). Also a study done by Senff NJ on 300 primary cutaneous B cell lymphomas showed that high expression of FOXP1 protein and round cell morphology is associated with unfavourable prognosis and is independent survival factor (16). This was

supported by another comparative study done by Espinet B. on 15 patients which showed that overexpression of FOXP1 is present in a considerable proportion of PCLBCL, leg type and might indicate an unfavourable prognosis(218). In the same study the authors also suggested the this overexpression was not related to mechanisms that lead to translocation (218).

MATERIAL AND METHODS

This 5 year study was carried out in Department of General Pathology, Christian Medical College and Hospital (CMCH), Vellore, India. The time period of the study was 1.5 years from the approval of study by ethical committee to August 2014. It is a partly retrospective and partly prospective study. The histopathological material (slides and blocks) were accrued from Department of General Pathology. This study included biopsy material of patients registered within CMCH and from those referred from outside. The clinical information and laboratory parameters were obtained from clinical workstation and charts from medical records department or from the biopsy request forms for outside referral cases.

Inclusion criteria:

All cases of primary cutaneous lymphomas diagnosed in our department from 1st May 2007 till 31st May 2012.

Exclusion criteria:

1. Cases on which further studies were not possible due to preservation or storage artifacts in the histopathological tissue material or paraffin embedded block. These cases were not included for special studies (For Notch-1 and Fox p1). However their clinic-pathological profiles were included in the study.

Parameters evaluated: In each patient the following parameters were recorded.

1. Morphological subtype: According to WHO/EORTC 2005(modified in 2008) classification{appendix 7}.

2. Clinical information: Age, sex, presence of itching (present or absent), disease presentation (patch, macule, papule, nodule etc.), duration of symptoms, organomegaly and lymphadenopathy.

3. Hematological and laboratory parameters: Complete blood counts including hemoglobin level, total leukocyte count(TLC), differential count(DC) and platelet count(PLC); serum lactate dehydrogenase (LDH) levels and erythrocyte sedimentation rate(ESR).

4. Tumor staging data: See appendix 8{ISCL-EORTC staging system}&10{Ann Arbor staging system}.

5. Special studies including bone marrow aspiration, trephine biopsy and TCR rearrangement studies (if done).

Tissue processing:

All tissue samples were fixed in 10% formalin and were processed in an automated processor for thirteen hours {Appendix 1} and embedded in paraffin wax. Four micron sections were cut and the slides were stained with haematoxylin and eosin (H&E) and mounted with DPX.

Immunohistochemistry was done for all cases on formalin fixed paraffin embedded tissue sections. It was done manually using the Envision technique developed with Diaminobenzidine {Appendix 3&4}. A primary panel of one pan T-cell marker {CD3}, one pan B-cell marker {CD20} and proliferation marker {MIB1} was used. In CD3 positive cases other markers were done for sub typing depending on the morphology which included pan T-cell antigens CD5 and CD7 and subset markers CD4 {helper T cell antigen} and CD8 {cytotoxic T cell antigen}. NK cell antigen

CD56 and EBV antigen LMP-1 were done for cases with clinical and morphological findings suggestive of NK/T cell lymphoma. Activation marker CD30 and ALK epithelial membrane antigen (EMA) were done for cases with morphology and clinical background of CD30 lymphoproliferative neoplasms.

Two additional markers were done for T cell lymphomas and B-cell lymphomas named Notch-1 and Foxp-1 respectively for prognostification.

The details of the antibody panels used including their clones, source, dilution and pre-treatment have been shown in appendix 2. Procedure of Immunohistochemistry has been shown in appendix 3. Preparation of reagents for Immunohistochemistry has been shown in appendix 4. All H&E sections and immunohistochemistry slides were reviewed and reclassified if necessary.

Staging: Mycosis fungoides were staged according to the criteria proposed by ISCL-EORTC {Appendix 8}. All other cutaneous lymphomas were staged according to modified Ann Arbor staging system {Appendix 10}. The international prognostic Index {IPI} of lymphomas {Non MF/SS} was also included in the study {Appendix 11}.

Statistical Analysis: Data entry and all statistical analysis were done using Epi-info software. Descriptive statistics such as frequency and percentage were used. Categorical variables were analysed using $\chi 2$ test with Yates continued correction and Fischer's exact test. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 115 cutaneous lymphomas were diagnosed, out of 11320 skin biopsies, during 5 years {01/05/2007 to 31/05/2012} in the Department of General Pathology, Christian Medical College Hospital. The frequency of cutaneous lymphoma in our study was 1.01 per 100 biopsy specimen {115 per 11320}. This lymphoma comprised 9% {115 of 1164} of all extra nodal Non-Hodgkin's lymphomas in the same duration {Fig 3}. Of these 89% {102 of 115 cases} were cutaneous T cell lymphoma {CTCL}, 6% {7 of 115 cases} were cutaneous B cell lymphoma{CBCL} and 0.9% {1 of 115 cases} were Blastic plasmacytoid dendritic cell neoplasm{BDCN}{fig 4}.

Figure 3 : FREQUENCY OF CUTANEOUS AND NON HODGKIN LYMPHOMA (NHL) OVER A PERIOD OF 5 YEAR PERIOD IN CMC HOSPITAL.

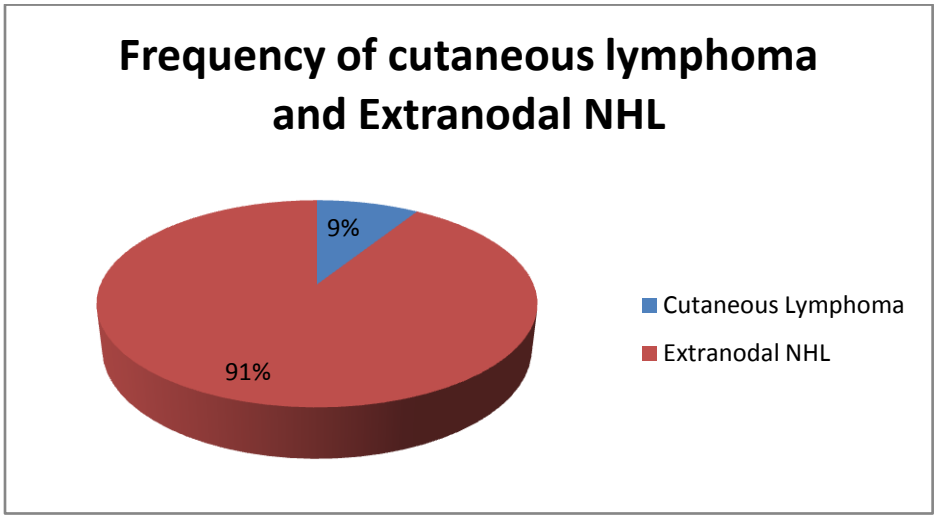
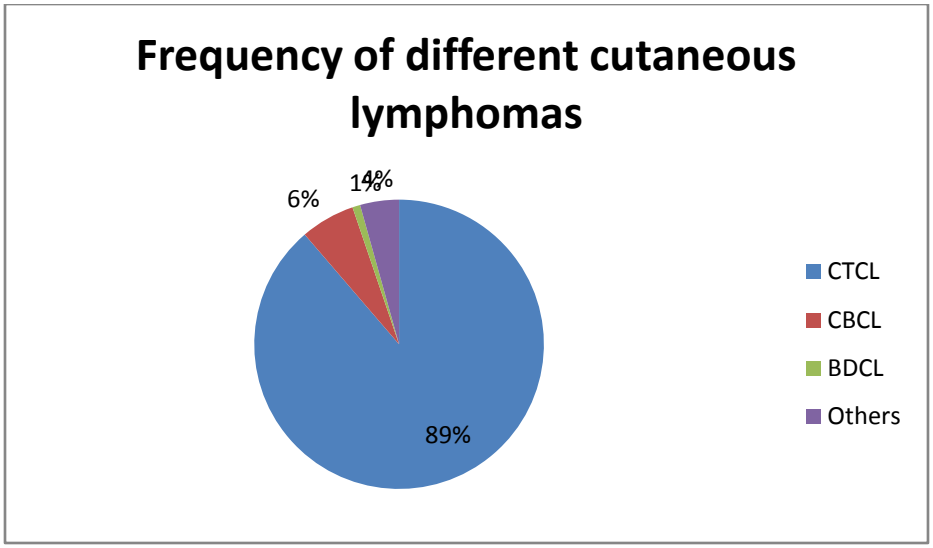


Figure 4: FREQUENCY OF MAJOR CATEGORIES OF CUTANEOUS LYMPHOMAS DURING 5 YEAR PERIOD IN CMC HOSPITAL.



Of these, Mycosis fungoides comprised 44 % {51 cases} followed by SPTCL 21% {24 cases} and CD 30 positive lymphoproliferative disorder 17.4% {20 cases}.

Age and Sex ratio: The median age of presentation was 39 years {range 3 to 88 years}. More than 35% of the cases were seen in 4^{th} – 6^{th} decade {fig 5}. There was a male preponderance with M:F ratio of 1.19:1{fig. 6}. Pediatric {<18 years} cutaneous lymphomas constituted 15.6% {18 of 115 cases}. Of these the most common was mycosis fungoides {44.4%} followed by SPTCL {33.3%} and ALCL {11.1%} {fig. 7}. There was a female preponderance in pediatric lymphoma with M:F ratio of 0.8:1.

Figure 5 :**FREQUENCY OF ALL CUTANEOUS LYMPHOMAS ACCCORDING TO AGE {N=115}.**

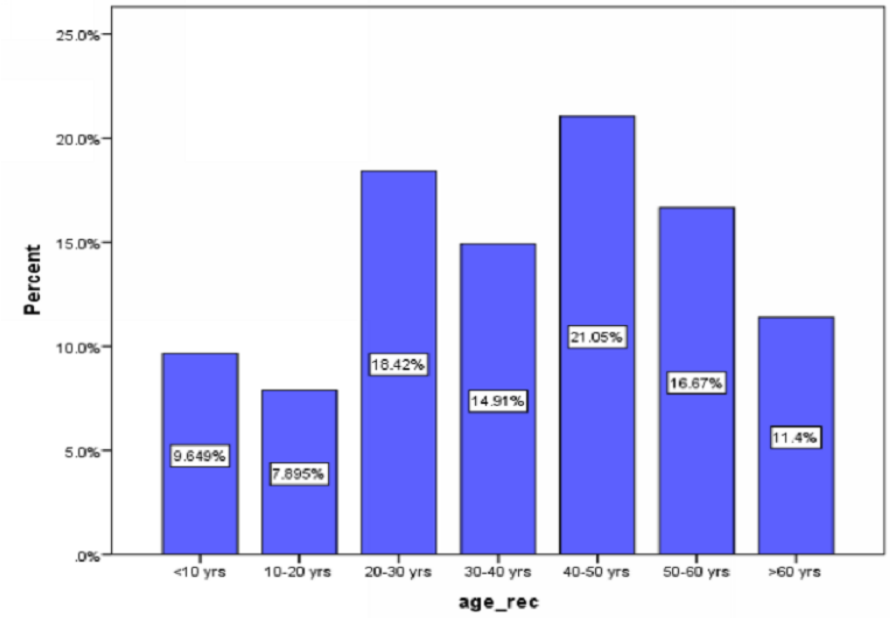


Figure 6: OVERALL SEX DISTRIBUTION IN CUTANEOUS LYMPHOMA.

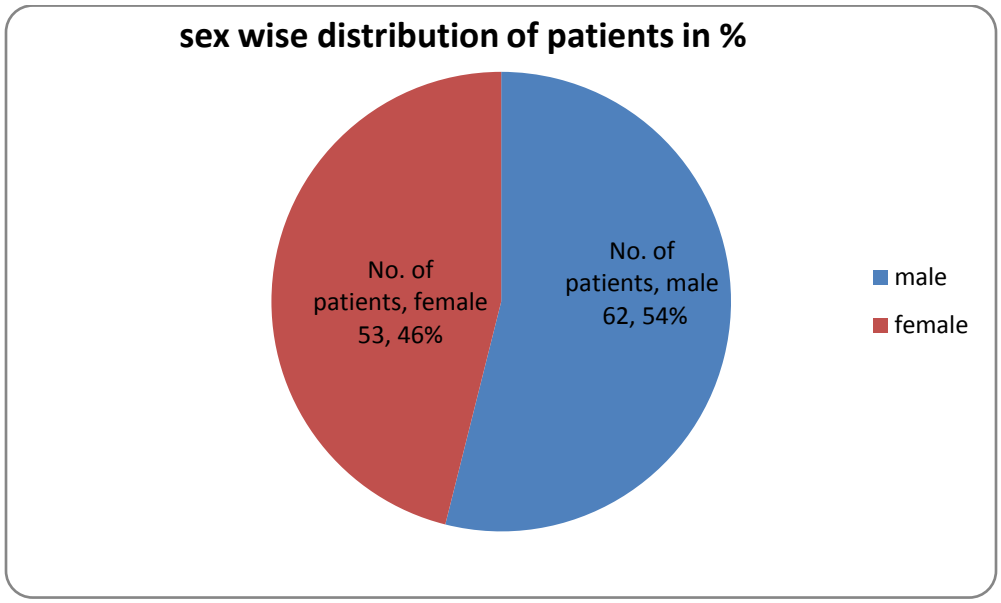
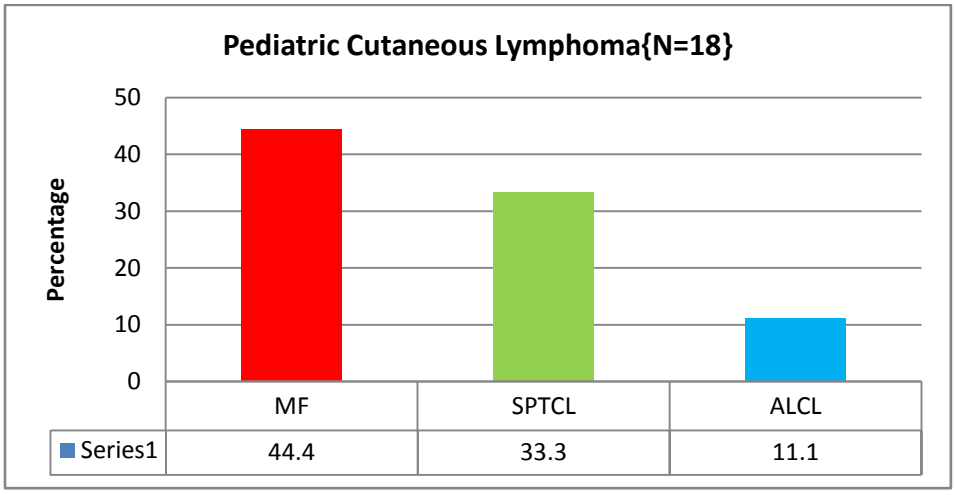
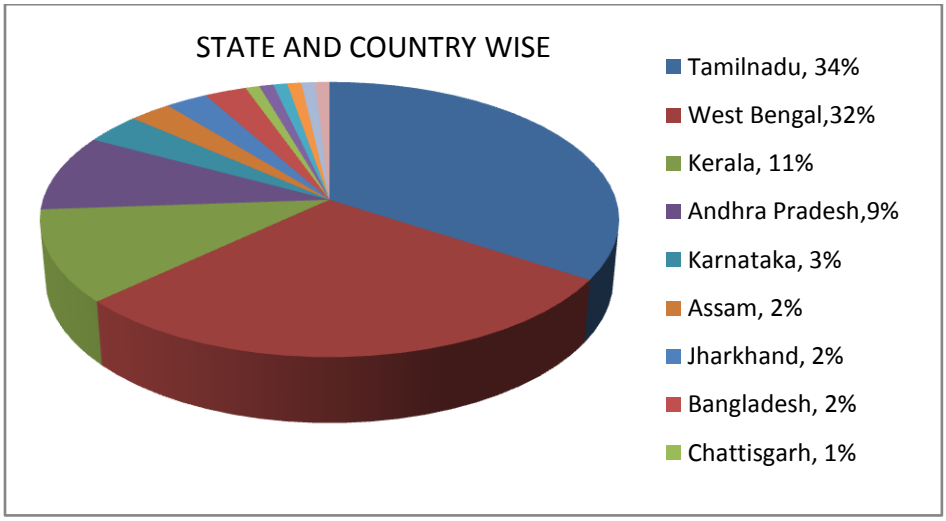


Figure7: **FREQUENCY OF PEDIATRIC CUTANEOUS LYMPHOMAS IN PERCENTAGE.**



Geographic location: As a tertiary care center, most of the patients were referred from other institutes and from different states. Data of 111 patients were available, out of which, majority were from Tamil Nadu {34%} and West Bengal {32%}. From other countries three patients were referred from Bangladesh and one each from Nepal and Sri Lanka. The detailed geographic location and pattern are depicted in {Figure 8}.

Figure 8: FREQUENCY OF PATIENTS REFERRED FROM DIFFERENT STATES AND COUNTRIES DURING A STUDY.

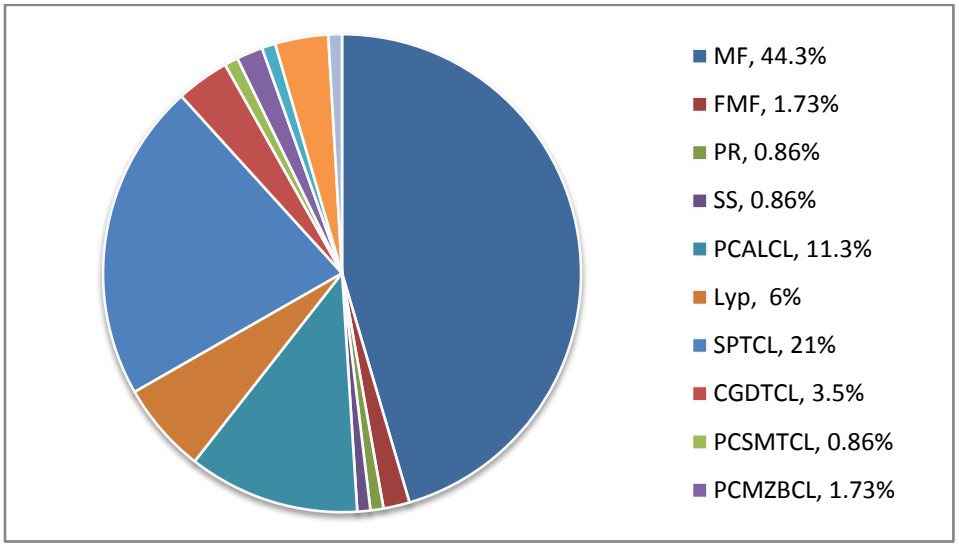


Frequency of subtypes of cutaneous lymphomas{Table 1}: Mycosis fungoides was the most common subtype of all cutaneous lymphomas comprising 44%, followed by SPTCL-21% and cutaneous CD30 positive lymphoproliferative disorder comprising 17%{Fig 9}.

Table 1: NUMBER AND FREQUENCY OF SUBTYPES OF CUTANEOUS LYMPHOMASIN OUR STUDY {N=115}.

Sr. no	Types	Number	Frequency
1	Mycosis Fungoides{MF}	51	44.3%
	Folliculotropic MF{FMF}	*02*	*1.70%*
	Pagetoid reticulosis{PR}	*01*	*0.86%*
2	Sézary Syndrome{SS}	01	0.86%
3	Cutaneous CD 30 positive lymphoproliferative disorder	20	17.3%
	Primary Cutaneous ALCL{PCALCL}	*13*	*11.3%*
	Lymphomatoid Papulosis{LyP}	*07*	*6.08%*
4	Subcutaneous Panniculitis like T-cell lymphoma{SPTCL}	24	20.9%
5	Extranodal NK/T cell lymphoma, nasal type	01	0.86%
6	Cutaneous Gamma Delta T cell lymphoma{CGDTCL}	04	3.47%
7	Cutaneous CD4 positive small/medium sized pleomorphic T cell lymphoma{PCSMTCL}	01	0.86%
8	Primary cutaneous marginal zone B cell lymphoma{PCMZBL}	02	1.73%
9	Primary cutaneous follicle center lymphoma	01	0.86%
10	Primary cutaneous diffuse large B cell lymphoma, other	04	3.47%
11	Blastic plasmacytoid dendritic cell neoplasm	01	0.86%
12	Other cases	05	4.34%

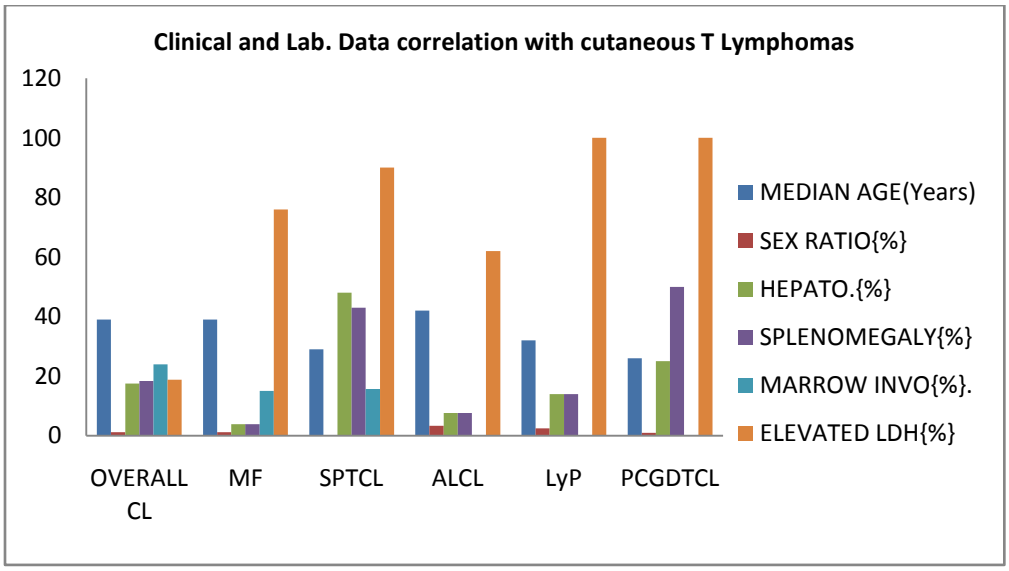
Figure 9: FREQUENCY OF SUBCATEGORY OF VARIOUS CUTANEOUS LYMPHOMAS.



Sites of involvement: The most common sites of presentation were trunks and extremities.Non photo exposed areas accounted for 56% followed by trunks, extremities, head and neck region {Non photo exposed areas and photo exposed areas} 36% and scalp, head and neck region {Photo exposed areas, 8%}. The frequencies of sites of involvement have been shown in fig. 9.

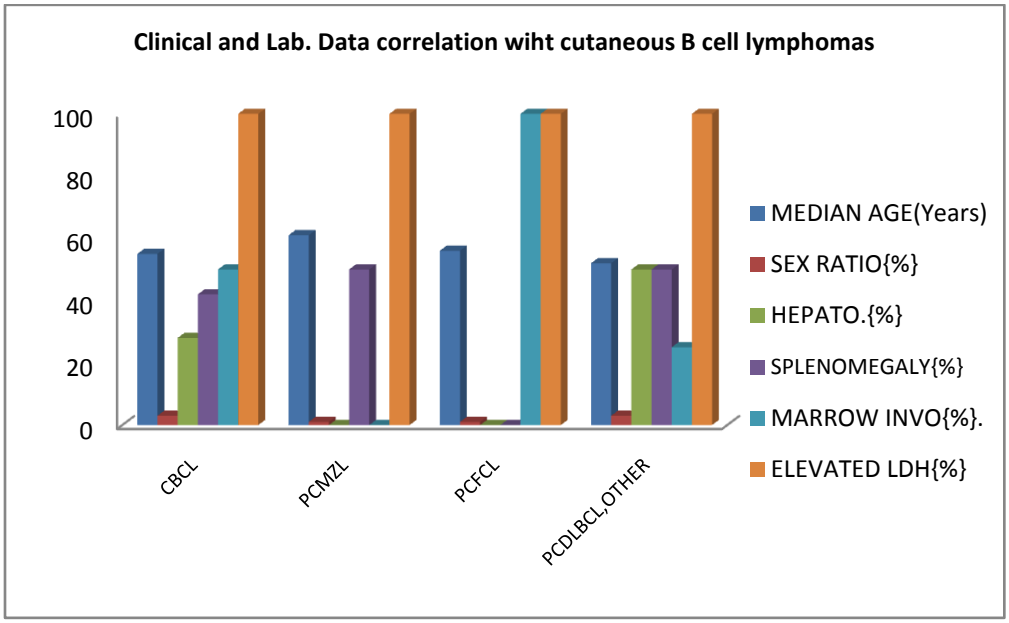
Clinical presentation and laboratory findings {Fig 10& 11}: Macules and patches were seen in 29% followed by nodules 28% and plaque 26%. Fever was present in 18.4% and edema (pedal, periorbital and generalized edema) was present in 8.7%. Hepatomegaly was seen in 17.5% and splenomegaly in 18.4%. Marrow involvement at presentation was seen in 24%. Anemia was a common manifestation and seen in 33.7%. Leucopenia was seen in 19.2% and thrombocytopenia in 18.6%. Serum LDH levels were elevated in 18.8%.

Figure 10: CLINICAL AND LABORATORY DATA CORRELATION OF CUTANEOUS T CELL LYMPHOMAS.



CT:Cutaneous Lymphomas, MF:Mycosis Fungoides, SPTCL:SubcutaneousPannicultis like T cell lymphomas, LyP: Lymphomatoid papulosis, PCGDTCL: Primary cutaneous gamma/delta T cell lymphoma.

Figure 11: CLINICAL AND LABORATORY DATA CORRELATION OF CUTANEOUS B CELL LYMPHOMAS.



CBCL:Cutaneous B cell lymphoma, PCMZL: Primary cutaneous Marginal zone lymphoma, PCDLBCL, other: Primary cutaneous diffuse large B cell lymphoma, other.

Staging and IPI{International Prognostic Index}: We used the ISCL/EORTC staging system {Appendix 7} for MF/SS and Ann Arbor staging system {Appendix 9} for other cutaneous lymphomas. Of the available data on 49 MF cases, 80% were in stage TIA/TIB at presentation whereas the remaining 20% were in stage TII, TIII and TIV {Fig. 12, Table 2}. Ann Arbor staging was done for non MF/SS cases, in which 80-90% were in the stage I category and the remaining were in the stage IV category {Table 3}. IPI scoring{Appendix 10} was available in 41{Non MF/SS cases} cases and accordingly the risk categories were stratified as low risk in 12% {5 of 41 cases}, low intermediate in 68% {28 of 41 cases} and high intermediate in 20% {8 of 41 cases} stratified for each subcategories {Fig. 13, only for SPTCL & ALCL, Table 4}.

Table 2: ISCL/EORTC STAGING FOR MF/SS.

Stage	**MF** **N=49**	**SS** **N=1**
Stage IA Stage IB	6.2% 73.4%	-- --
Stage II	8.16%	--
Stage III	2%	--
Stage IV	10.2%	100%

Figure 5: ISCL-EORTC STAGING FOR MF/SS.

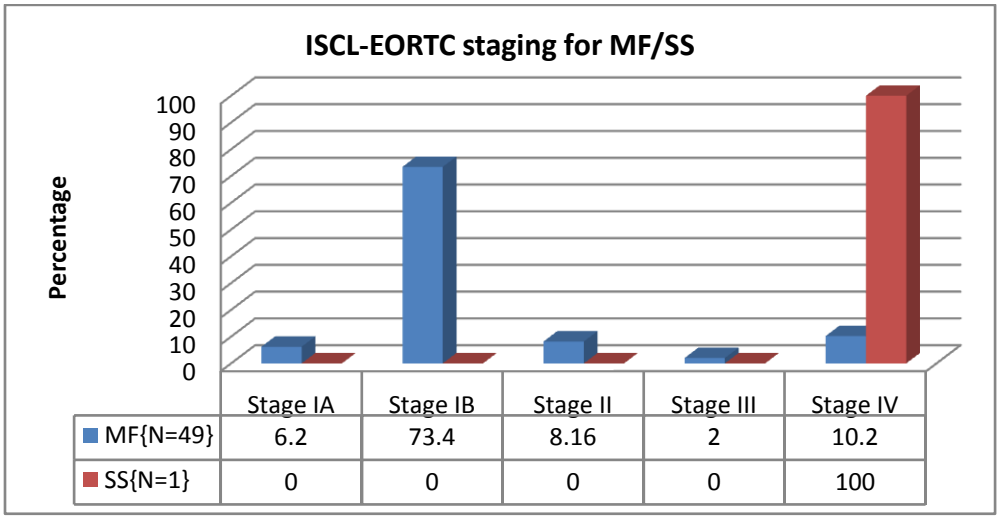


Table 3: ANN ARBOR STAGING OF CUTANEOUS LYMPHOMAS (EXCLUDING MF AND SS)

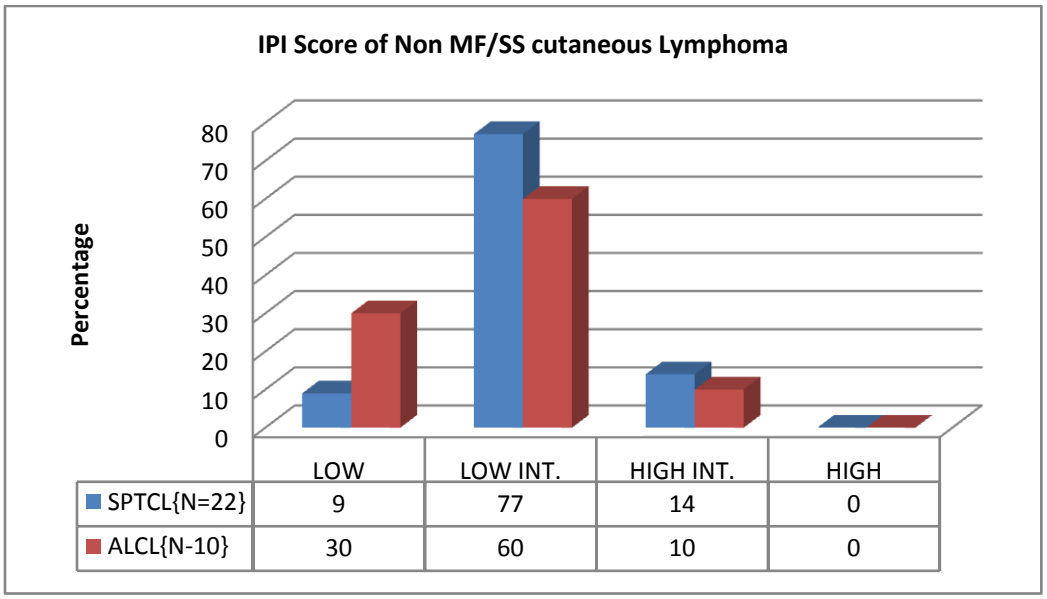
Stage	SPTCL N=23	ALCL N=13	LyP N=6	CGDTCL N=4	CMZBCL N=2	CDLBCL, other N=4
Stage I	86%	92%	100%	75%	50%	25%
Stage II	--	---	---	---	---	---
Stage III	--	---	---	---	---	---
Stage IV	14%	08%	---	25%	50%	75%

Table 4: INTERNATIONAL PROGNOSTIC INDEX {IPI} OF CUTANEOUS LYMPHOMAS (EXCLUDING MF/SS)

IPI	SPTCL N=22	ALCL N=10	LyP N=2	CGDTCL N=3	CMZBCL N=2	CDLBCL, other N=2
Low	9%	30%	---	---	---	---
Low Intermediate	77%	60%	100%	100%	---	---
High Intermediate	14%	10%	---	---	100%	100%
High	---	---	---	---	---	---

N=number of patients with available data.

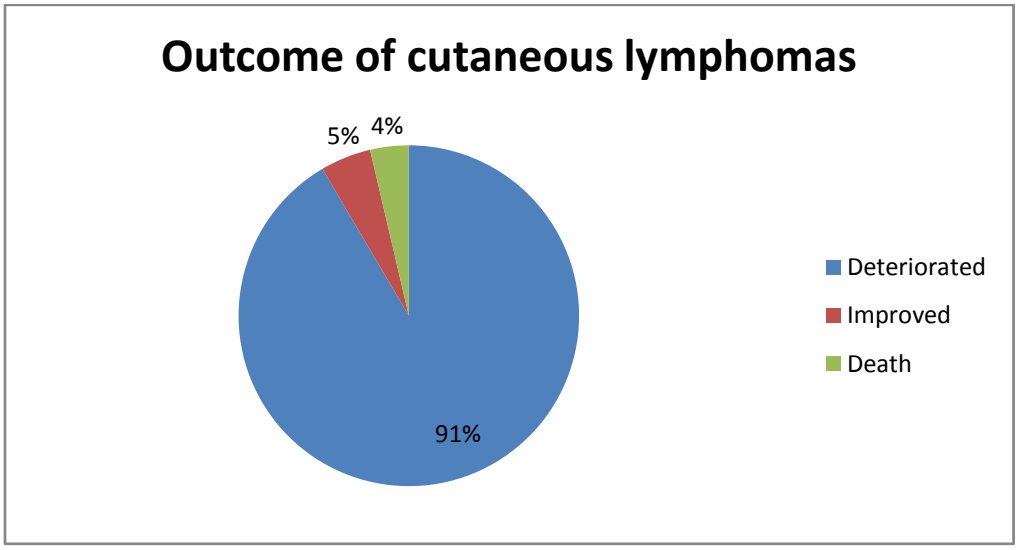
Figure 13: INTRERNATIONA PROGNOSTIC INDEX SCORE OF NON MF/SS CUTANEOUS LYMPHOMAS.



Treatment: Most of the patients with Mycosis fungoides received local application {20 of 38 cases} and in few cases UVB/PUVA {10 of 38 cases}. Only few resistant cases received EBT (External beam therapy){1 of 38 cases} and chemotherapy {7 of 38 cases} also. The rest of the cutaneous lymphomas were treated by CHOP, DHAP or CVP regimen {37 of 44 cases} based on tumor typing and presentation at arrival. Bone marrow transplantation (BMT) was done in two patients.

Treatment outcome and follow up: Follow up data was available in 82 patients. The mean follow up period was 21 months {Range 1-104 months}. During follow up 91.4% either developed new lesions or the older lesions persisted, 4.8% showed regression of lesions and 3 patients died of cutaneous lymphoma {3.65%}. {Fig. 14}

Figure 14: FREQUENCY OF OUTCOME OF DIFFERENT CUTANEOUS LYMPHOMA.



CUTANEOUS T CELL LYMPHOMAS

MYCOSIS FUNGOIDES

Frequency: Mycosis fungoides comprised 44% of all our cutaneous lymphomas. It also accounted for 50% of the CTCLs and was the most common subtype of cutaneous T-cell lymphomas in our study.

Age and sex ratio: The median age of presentation was 39 years {range 3-75} with a slight male preponderance {M:F ratio of 1.2:1}.

Sites of involvement: Most of the patients presented with generalized skin lesions. There was overlap in sites in involvement. The most common sites involved were extremities and trunk seen in 57% followed by entire body involvement including photo exposed and non-photoexposed areas seen in 17%. Back (6), chest (1), scalp (2), neck (4), buttocks (1) and perianal region (1) were also involved. {Fig. 17}

Clinical presentation: Patch stage was the most common presentation of MF, seen in 68% followed by plaque in 20% and tumor stage seen in 12%{Fig. 18}. Patients with patch stage presented with generalized skin lesions which included patches, papules and macules. Patients with tumor presented with plaques and multiple subcutaneous nodules with ulceration. B symptoms were seen only in two patients. Eleven cases showed lymph node enlargement, biopsy was available only for two cases for histopathological examination, out of which one was positive for lymphoma {MF in tumor stage}. Bone marrow was performed in 13 cases, out of which two were positive for lymphoma involvement {15%}. Majority of the cases were ISCL/EORTC stage 1{1A&1B} with 81% followed by 10% in stage 4.

Morphology: Patch stage {34 cases} – Most of the patients showed hyperkeratosis and acanthosis of epidermis {30 of 34 cases} with parakeratosis in some cases. The most consistent feature was epidermotropism seen in almost all the cases with tagging of atypical lymphoid cells along the basal layer seen in 94%. A patchy lichenoid infiltrate with basal cell vacuolation was seen in 8%. Haloed lymphocytes were seen in 64%. Intraepidermal collections of atypical cells {Pautrier's microabscesses} were seen in 18%. Folliculotropism was seen in 6%. The infiltrate extended into the superficial dermis in 91%. Other less common features seen were pigment incontinence {21%}, edema, extravasated RBCs {5%}, colloid bodies in the epidermis {8%} and multinucleated giant cells with occasional granulomas {10%}. One case showed increased intradermal mucin, another showed karyorrhectic debris and a third showed string of beads appearance (Pagetoid appearance).

Plaque stage**:** {10 cases} Majority of the patients presented in Stage II {7 of 10 cases, 70%} with predisposition to involve extremities and trunk (Non photoexposed region){8 of 10 cases}. The scalp and neck region was involved in two cases. Erythematous lesions were present all over the body in one case. On histomorphology the epidermis was hypertrophied in 57%, normal in 28% and flattened in 14% of cases. Epidermotropism was present in 70% of the cases. Almost all cases showed superficial perivascular and interstitial infiltrates. Apart from the epidermis, the atypical lymphocytes involved adnexa {2 cases}, follicles {2 cases} and lobules {1 case}. None of the cases showed features of vasculitis. Pautrier's microabscesses were present in 20%. Other less common features were clusters of epithelioid histiocytes {3 cases}, lichenoid infiltrate {1 case}, and intra epidermal vesicle {1 case} and necrosis admixed with karyorrhectic debris {1 case}.

Tumor stage {6 cases}: All cases showed a pan dermal infiltrate of neoplastic lymphoid cells as described. Pautrier microabscesses were seen in 1 of the 6 cases. Large cell transformation was seen in three of the six cases wherein large cells comprised more than 25% of the cell population. Only one case showed involvement of head and neck region in addition to extremities and trunk. Mild hepatosplenomegaly was present in two cases (not biopsied). One patient showed lymph node involvement. Surface ulceration was present in two cases and brisk mitosis, apoptosis and necrosis were present in three cases.

Variants: Patch stage {68%} was the most common phase. Clinically and histomorphologically hypopigmented variant was the most common (53 %), followed by poikilodermic {6%}, folliculotropic {4%} and one each for pagetoid reticulosis and erythrodermic MF. All pediatric

MF cases {8 cases} were hypo pigmented. Blocks were available only for four cases, out of which 50% were positive for both CD4/CD8 and 25% were positive for CD8 and CD4 each.

The differentials given clinically for hypopigmented Mycosis Fungoides were Hansen's disease {8 of 26 cases} and Vitiligo {6 of 26 cases} followed by parapsoariasis. The hypopigmented MF diagnosis was accurately suspected clinically in 4 cases only. Early MF was diagnosed in 30 cases {59%} based on criteria as described by Pimpinelli et al. {Appendix 8}. The overall numbers and frequencies of each subtypes of MF are given in Table 5.

Table 5 : MYCOSIS FUNGOIDES (MF) VARIANTS IN OUR STUDY {N=51}.

SR.NO.	MF VARIANTS	NUMBER	FREQUENCY
1.	Hypopigmented	26	53%
2.	Patch	8	16%
3.	Plaque	5	10%
4.	Poikilodermic	3	6%
5.	Transformed MF	3	6%
6.	Folliculotropic	2	4%
7.	Erythrodermic	1	2%
8.	Pagetoid reticulosis	1	2%

Immunohistochemistry: All our cases had a CD3+, CD20- and CD7- immunophenotype. CD4 was positive in 52%. A predominant CD8+ phenotype was seen 8 cases. Both CD4 and CD8 positivity is seen in two cases. Large cells were CD30+ in two of the three cases with large cell transformation.

Treatment and Follow up: Data was available for 38 patients. Majority of the patients received localized therapy in the form of steroids and PUVA/UVB {78%} followed by systemic multiagent chemotherapy {either CHOP/CVP/DHAP} given in 18% cases, out of which one patient received bone marrow transplantation {3%}. 75% of the patients with CD8 positivity were stable during

mean follow up of 15 months. Of the hypopigmented MFs 62% showed improvement during a mean follow up of 23 months. Five of the hypopigmented variants were CD8 positive, and all showed improvement with localized therapy. Only one patient showed bone marrow involvement with progressive deterioration. All juvenile MF cases were in stage IA with progressive improvement, except one patient who presented in stage IB with progressive deterioration of symptoms during 81 months of follow up. Those with Pautrier's microabscesses showed deterioration during 21 months of follow up with one requiring systemic chemotherapy. This was not statistically significant as numbers were small.

SEZARY SYNDROME

There was one case of Sézary syndrome diagnosed in a 42 year old male referred from Bangladesh, constituting 0.9% of all the PTCLs. Patient presented with itching all over the body, erythroderma, alopecia, nail atrophy and generalized lymphadenopathy. Peripheral smear showed marked leukocytosis (90,700/cumm) with 71% atypical lymphoid cells {absolute Sézary cell count – 6440 cells/cu mm}. Skin, lymph node (inguinal) and bone marrow trephine biopsy were done which showed involvement by lymphoma. Accordingly the ISCL-EORTC staging was stage IIIA {T4N2M0}. Morphologically, skin showed pan dermal infiltrates of small to medium sized lymphoid cells with scant cytoplasm and irregularly contoured nuclei. Periadnexal, perifollicular and perivascular infiltration were seen. Focal Pautrier's micro abscess formation was also present. Mild hepatomegaly was present. Serum LDH was elevated (1502 U/L). The immunophenotype of the neoplastic cells was CD3+, CD4+, CD8- and CD30-. Lymph nodes were involved by lymphoma and showed evidence of a few large cells which on

immunohistochemistry showed positivity for CD30. Bone marrow trephine biopsy also showed involvement by lymphoma. Patient was treated with local therapy (PUVA) and systemic multi agent chemotherapy (CHOP) for one month. The lesions were persisting during a month of follow-up.

SUBCUTANEOUS PANNICULITIS LIKE T-CELL LYMPHOMA

Frequency: Subcutaneous panniculitis like T-cell lymphoma comprised 21% of all cutaneous lymphomas.

Age and sex ratio: The median age of presentation was 29 years {range 3-56 years} and was predominantly seen in females with a M:Fratio of 1:4.7.

Sites of involvement: Most patients presented with multiple subcutaneous nodules of varying sizes. Lower extremities were the most common site of involvement followed by upper extremities and trunk {17 of 22 cases}. Marrow involvement was present in 17%.

Clinical presentation and laboratory findings: B symptoms were seen in 75%. Hepatomegaly was seen in 47% and splenomegaly in 43%. Hepatosplenomegaly was seen in 34%. Anemia was seen in 43%, leucopenia in 39% and thrombocytopenia in 26%. Pancytopenia was seen in 13%. Bone marrow was involved in 15%. Serum LDH level was elevated in 78%. Serum LDH of > 1000 units was found in 11 patients. Angiocentricity and angioinvasion were found in two patients who were CD56 negative. Both of the patients had hemophagocytosis. Bone marrow was involved in two cases with raised LDH levels{mean 2163 Units/L} and both showed

deterioration of symptoms during mean follow up of 25 months though this association was not statistically significant .

Ann Arbor Staging and International Prognostic index: 86% of the patients presented with stage I disease suggesting localized disease and 77% {Table 8} belonged to low intermediate{LI} risk category. There was no significant association with organomegaly, hemophagocytosis or pancytopenia.

Morphology: There was a predominant subcutaneous lobular neoplastic lymphoid infiltrate with sparing of the dermis and epidermis. Characteristic rimming of fat spaces by the neoplastic cells was seen in 86%. The infiltrate extended into the deep dermis in 56% with evidence of periadnexal infiltration. Minimal infiltration of the mid/upper dermis was seen in 2 cases but none of the cases showed epidermotropism. Reactive background comprising lymphocytes, plasma cells and histiocytes was seen in almost all cases. Characteristic “bean bag” histiocytes were present with evidence of phagocytosis of nuclear debris in 65%. Necrosis was commonly found and seen in 47%. One case showed angioinvasion and one more case showed angiocentricity with transmural inflammation. Four cases showed aggregates of histiocytes and multinucleate giant-cells.

Immunohistochemistry: All the cases were CD3+, CD8+ and CD20- with an average MIB1 labeling index of 40-50%. CD56 was focally positive in 5%. Cytotoxic granule associated protein granzyme B was positive in 88%.

Treatment and follow up: The treatment and follow up data was available for 19 patients. Majority {89%, 17 of 19 cases} received systemic multiagent chemotherapy {CHOP/CVP/DHAP}.

Two patients received steroids during first OPD visit {diagnosis was not available}, these patient did not come during follow-up. The median follow up period of 20 patients was 19 months {Range 1-80 months} during which 15 patients developed new lesions and/or deteriorated symptomatically {75%}, 4 remained stable {20%) and 1 patient improved {symptomatically/clinically} {5%}. Out of 11 patients with raised LDH {more than 1000 units/litre}, 10 patients received chemotherapy {data of one patient was not available}. Almost all patients showed deterioration {either developed new lesions and/or worsening of symptoms} {9 of 10 patients}. Follow up was available of one patient with CD56 positivity, who showed deterioration of symptoms during 24 months of follow up.

CUTANEOUS CD30 POSITIVE LYMPHOPROLIFERATIVE DISORDERS

Frequency: There were 20 cases of cutaneous CD30 positive lymphoproliferative disorder amounting to 17% of all cutaneous lymphomas. Of these, 13{11.3%} were primary cutaneous anaplastic large cell lymphoma {ALCL} and the remaining 7{6%} were LyP.

Age and sex ratio: The median age of presentation was 38 years {range 5-70 years}. The median age of diagnosis for ALCL was 42 years and for LyP was 31 years. As with MF there was male predominance with a M:F ratio of 3:1.

Clinical features, morphology, Immunohistochemistry, treatment and follow up:

1. Cutaneous ALCL: Most of the patients presented with localized disease in the form of papules, plaques and nodules. B symptoms were seen in 23%. One case had mild hepatosplenomegaly and lymphadenopathy. Total six cases had lymphadenopathy, however

biopsy was not done. On histopathological examination there was a pan dermal infiltrate of medium to large sized lymphoid cells similar to those seen in systemic ALCL. Hallmark cells were seen in 4 of 13 cases {31%}. Epidermotropism was seen in one case. On immunohistochemistry the neoplastic cells were CD3 +, CD30+(>75% of atypical cells} and ALK-negative. One case was ALK positive{cytoplasmic and focal nuclear} with a MIB1 labeling index of 80-90%. One case showed positivity for CD4, CD8and CD56{focally and weak}. The follow up data of this patient was not available.Nine cases were treated here with multiagent chemotherapy {CHOP, DHAP or CVP}. The mean follow up period was 26 months. Out of nine patients, seven developed new lesions during follow up, one had stable lesions with only mild symptomatic improvement and another showed progressive improvement. The patient who improved, though he had organomegaly and small lymph nodes was ALK positive with multinucleate, multilobate histology.

2. Lymphomatoid papulosis: All the seven patients presented with recurrent papules and plaques. B symptoms were seen in 33%. On histopathological examination, skin showed a wedge shaped infiltrate similar to LyP type A within the upper and mid dermis. The epidermis was normal in three cases (42%), hypertrophied in two cases (28%) and flattened in one case (14%). In one case the epidermis displayed ulceration and was replaced by inflammatory exudate. Epidermotropism was seen in one case. On immunohistochemistry, the small to medium sized lymphoid cells were CD3+. The larger cells were CD30+ and amounted to 10-20% of the neoplastic cells. Average MIB1 labeling index was 10-15%. Mild hepatosplenomegaly and lymphadenopathy were present in one patient who was young and during subsequent follow up the symptoms improved symptomatically. Vascular proliferation and admixed eosinophils

and histiocytes were seen in 57%. Vasculopathic features were present in one case. The treatment details and follow up were available in three patients. The mean follow up period for these patients was 10 months. One patient improved with reduction of lesion, another was stable with no change in lesions and a third deteriorated and developed new lesions. There was marked elevation of LDH levels in the patient with deterioration and during follow up this patinet was shifted to systemic multiagent chemotherapy. Two patients were treated with steroids and one patient with steroids and UVB/PUVA therapy. Prognosis was affected by IPI and not by organomegaly, bone marrow involvement or deranged hematological parameters.

PRIMARY CUTANEOUS GAMMA DELTA T-CELL LYMPHOMA

Frequency: There were four cases of primary cutaneous gamma delta T-cell lymphoma which comprised 2.6% of all our cutaneous lymphomas.

Age and sex ratio: Three were 25 year old and one was a 30 year old male patient. The M:F ratio was 1:1.

Site of involvement: All 4 patients presented with recurrent plaques and subcutaneous nodules with ulceration predominantly distributed in the upper and lower extremities. Bone marrow was done in three cases and not involved in any of the cases.

Clinical presentation and laboratory findings: One patient presented with chest pain, low grade fever, loss of weight and mild splenomegaly. Same patient was found to have pleural effusion and serologically positive for hepatitis A. Another patient had pleural effusion, pedal edema and ascites and the remaining one had periorbital edema. Clinical detail of one patient

was not available. LDH was done in three patients and found to be moderate to markedly increased {Mean value 1551 Units/litre}. B symptoms {fever, night sweat and weight loss} were seen in two patients.

Ann Arbor Staging and International Prognostic index: Two cases were in stage I and two were in stage IV. All cases were in low intermediate risk category according to prognostic index.

Morphology: Morphology was similar to SPTCL with dermal and subcutaneous infiltrate of atypical lymphoid cells. The infiltrate focally extended upto mid and superficial dermis in two cases where it surrounded adnexa. Admixed were seen numerous histiocytes and necrotic material. Rimming of adipocytes and cytophagocytosis were present in all three cases. Angioinvasion was present in one case who was incidentally CD 56 negative. The epidermis was not evaluated in one case due to epidermal necrosis. In the remaining cases there were no epidermotropism.

Immunophenotype: All the cases were CD3+ with a MIB1 labeling index of 75-80%. CD8 and CD56 were positive in one of the three cases. In view of the morphology and high MIB-1 index, TCR gene rearrangement was advised to all patients. However due to economic constraints only one patient could afford it {which shows clonality for T cell gamma chain}. This patient was CD56 negative and showed no angioinvasion. The other patients were given diagnosis in favor of this variant.

Treatment, follow up and outcome: The follow up was available for two patients. The mean period of follow up was 11 months. One patient was treated with CVP regimen and the other patient who was CD56 positive with CHOP followed by DHAP regimen. Both patients showed

deterioration of symptoms with development of new lesions. The patient with CD56 positivity did not have angioinvasion, however he deteriorated during follow up(20 months). The patient with TCR gamma gene rearrangement developed new lesions during follow up (12 months). Only significant finding in this patient was marked raised LDH {2084 Units/L} compared to others in this group.

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

Frequency: Only one case of extra nodal Natural killer/T-cell lymphoma, nasal type(NKTCL) was present which constituted 0.8% of all cutaneous lymphomas.

Age and Sex: Twenty three year old male patient came from Andhra Pradesh for diagnosis and treatment.

Site of involvement: There were multiple lesions on both legs and on right thigh.

Clinical presentation and laboratory findings: The patient presented to the ER with painful plaques on both legs and necrotizing lesion on right thigh, which was present for the last 8 months and aggregated in last few days. Mild ascites, mild splenomegaly and generalized lymphadenopathy (cervical, mesenteric and inguinal) were also present. There was moderate anemia with leukopenia. The LDH was markedly elevated {4230 Units/Litre}. Bone marrow was done and it showed involvement by atypical lymphoid cells.

Ann Arbor Staging and International Prognostic index: This patient presented with stage III disease with a prognostic index of high intermediate category.

Morphology: There was dense pan dermal diffuse infiltrates of atypical lymphoid cells which extended to lobules of subcutis as well as up to the epidermis. The infiltrates also surrounded mid dermal vessels, adnexae and deep dermal nerves. Multinucleated and bizzare forms were present. Overlying epithelium shows acanthosis, ulceration and intraepidermal vesicle. Mitosis was brisk and a focus of necrosis was present.

Immunophenotype: The atypical lymphoid cells were positive for CD3 and CD56. Cytotoxic protein TIA-1 was positive. Latent membrane protein-1 (EBV-LMP), CD8 and CD30 were negative. As histomorphology, clinical presentation and Immunohistochemistry favored this variant, the diagnosis was given as consistent with extra nodal NK/T cell lymphoma, nasal type, though EBV-LMP was negative.

Treatment, follow up and outcome: After admission and diagnosis patient received four cycles of chemotherapy (CHOP) and local radiation (23 fractions). Despite continuous therapy the patient developed new lesions and died of septicemic shock one month after admission.

PRECURSOR HEMATOLOGIC NEOPLASM

$CD4^+/CD56^+$ HEMATODERMIC NEOPLASM

Frequency: There was one case of CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma) which comprised 0.8% of all our cutaneous lymphomas.

Age and Sex: The patient was a 51 year old gentlemen from Kerala.

Site of involvement: The lesions involved the chest, back and both arms.

Clinical presentation and laboratory findings: Patient presented with erythematous plaques over chest, back and arms for the last 10 years. There was neither organomegaly nor lymphadenopathy. The laboratory parameters were within normal limits including complete blood count except for mild eosinophilia. The LDH was within normal limits. Bone marrow was done and showed no involvement by lymphoma.

Ann Arbor Staging and International Prognostic index: The patient was categorized into stage I disease with low risk IPI.

Morphology: There was non-epidermotropic dense diffuse pan dermal infiltrates of medium-sized cells with finely dispersed chromatin, indistinct nucleoli and scant cytoplasm. A grenz zone was present between the hyperkeratotic epidermis and dermal infiltrate. Mitotic activity was brisk and the tumor cells splayed collagen bundles.

Immunophenotype: The tumor cells were positive for CD3, CD4>CD8 and CD123. Few weak and faint CD56 and CD68 cells were present. CD30, CD7 and TdT were negative. The MIB-1 proliferative index was approximately 40%.

Treatment, follow up and outcome: Patient was treated with systemic multiagent chemotherapy (CHOP). The patient was in clinically remission phase after five cycles of chemotherapy. The original lesions were markedly reduced with symptomatic improvement. As patient wanted to continue treatment at local hospital, we lost follow up after two months.

PTCL-NOS

Polymorphous lymphoid infiltrate: probably CD30 + lymphoproliferative disorder.

A 23 year old female from Tamilnadu presented with complaints of multiple indurated papules and plaques over upper limbs, back and face since 12 months. The differentials on clinical examination were lymphocytoma cutis or Jessner's infiltrate. There was no organomegaly or lymphadenopathy. Other lab investigations and bone marrow aspiration were not done. On histopathological examination, there was a dense lymphocytic infiltrate around vascular channels, hair follicles and sweat glands, seen predominantly throughout the dermis and also in the subcutis. The epidermis displayed mild hyperkeratosis and low papillomatosis but no epidermotropism. There were no large cells. The lymphocytic infiltrate was composed of predominantly CD3 positive T cells, with few interspersed and aggregated CD20 positive B cells. Few cells were CD30 positive. There was no follow up available for the patient.

Intravascular T cell lymphoma (IVTCL):

A 43 year old gentlemen from Madhya Pradesh presented with complains of erythematous blanching macular rashes in a reticulate pattern over trunk and upper and lower limbs since 6 months along with fever, pedal edema and pleural effusion. Clinically the differentials were cutaneous lymphoma, collagen vascular disease, SLE and dermatomyositis. There was mild hepatosplenomegaly. The patient had pancytopenia with relative neutrophilia. Serum LDH was markedly elevated. Bone marrow biopsy showed involvement by lymphoma cells. On histological examination the epidermis was unremarkable and the dermis showed mild interstitial infiltrates of lymphocytes and plasma cells. The upper dermis shows a few blood

vessels containing few large markedly pleomorphic cells with scant to moderate amount of cytoplasm and hyperchromatic nuclei with irregular nuclear membrane and inconspicuous nucleoli. An occasional mitotic figure was seen. These cells were seen in the lumina of blood vessels. On immunohistochemistry, these atypical cells were positive for CD3 and CD43. CD56 was equivocal. Granzyme B was non-contributory. Cytokeratin, CD20, CD79a, CD4, CD8 and CD30 were negative. Patient was treated with CHOP and died within two months of follow-up.

Atypical lymphohistiocytic infiltrates:

A 45 year old female from Tamilnadu was referred with multiple plaques and nodules on extremities and trunk since 12 months. Other investigation and BMA was not done. The skin biopsy showed dermis containing a moderately dense perivascular, perineural and periadnexal infiltrate of lymphocytes, histiocytes, epithelioid histiocytes and numerous eosinophils. The eosinophils were also seen lying diffusely in the insterstitium. The infiltrate extended to the dermo-subcutaneous junction. There were no fungal microorganisms, acid fast bacilli or LD bodies. The epidermis shows hyperkeratosis, almost regular acanthosis and a thinned out granular layer. Immunohistochemistry showed many KP1 and CD68 positive cells admixed with CD3, CD4 positive T cells. CD8, CD20, CD30, MPO, CD56 are negative. Scattered S100 positive foamy histiocytes and occasional CD1a positive Langerhan's cells were also present. A few cells were also positive for TIA. MIB-1 proliferation index was around 50%. The follow-up data was not available.

Primary T cell leukemia/lymphoma of skin:

A 3 year old male from West Bengal presented with multiple nodular lesions on head since 3 months. Other clinical details and laboratory investigation data were not available. On histomorphological examination, there was pan dermal infiltrate of small sized atypical lymphoid cells {positive for CD3, CD7 and TdT} with fine chromatin and scant cytoplasm. The lymphoid infiltrate extended to subcutis with predominant involvement of lobular septa. Overlying epidermis appeared histologically normal with no epidermotropism. The follow up was not available.

CUTANEOUS B CELL LYMPHOMAS

Frequency of subtypes of cutaneous B cell lymphomas

Cutaneous B cell lymphomas comprised 6% of all cutaneous lymphomas. Diffuse large B cell lymphoma(DLBCL- leg type) was the most common subtype of all cutaneous B cell lymphomas comprising 57%, followed by primary cutaneous marginal zone lymphoma(PCMZL) which was 28%.. DLBCL- leg type and PCMZL constitute 3% and 1.7% of all cutaneous lymphomas respectively.

Geographic distribution: Two patients were from West Bengal, from Tamilnadu and 2 from Andhra Pradesh. One patient was from Kerala.

Sites of involvement: The most common primary site of presentation was trunk and extremities accounting for 57% followed by head and neck region 28% and sacral region. Secondary organ involvement {bone marrow} at presentation was seen in two of four cases (50%).

Clinical presentation and laboratory findings: The most common presenting symptom was multiple nodules seen in 85%. Fever was present in 42%. Mild hepatosplenomegaly and lymphadenopathy were present in two cases. Anemia was seen in 60%. Leucopenia was present in one patient and thrombocytopenia in another. Serum LDH levels were elevated in all cases.

Staging and IPI: Five of the patients presented in stage IV and 2 in stage I. Data was available for 5 patients who were categorized into the high intermediate international prognostic index (IPI).

Treatment: Treatment details were available for four patients. All patients received multiagent chemotherapy in form of CHOP.

Follow up and prognosis: Follow up data was available in 5 patients. The mean follow up period was 15 months {Range 6-35 months}. All patients developed new lesions with mild symptomatic improvement.

PRIMARY CUTANEOUS DIFFUSE LARGE B CELL LYMPHOMA- LEG TYPE (PCDLBCL-leg type)

Frequency: PCDLBCL constitute 57% of cutaneous B cell lymphomas and 3% of all cutaneous lymphomas. This category includes primary cutaneous diffuse large B cell lymphoma-leg type (PCDLBCL-leg), primary cutaneous diffuse large B cell lymphoma-other (PCDLCBCL-other) and primary cutaneous intravascular large B cell lymphoma (PCILBCL).

Age and sex: The mean age of diagnosis was 52 years {Range 42-60 years}. There was male preponderance with a M: F ratio of 3:1.

Sites of involvement: Extremities, trunk and lower back were the most common sites involved.

Clinical presentation and laboratory findings: All patients presented with multiple nodules over non-photoexposed areas. Fever was present in one patient. Mild hepatosplenomegaly and lymphadenopathy were present in two cases. Laboratory investigations were done in two patients. Anemia was present in both cases. Thrombocytopenia was present in one patient. LDH was moderately elevated in both cases,

Morphology: All patients showed diffuse pan dermal involvement by atypical medium sized lymphoid cells with hyperchromatic nuclei, few cells with visible nucleoli and scant cytoplasm. Overlying epidermis was normal in all cases and none of the cases show epidermotropism. The infiltrate involved adnexa in two cases and focally involved lobules of subcutis in one case. At low power in dim light vague nodularity was appreciated in one case with focal germinal center formation. Mitosis and apoptotic activity were increased in three cases.

Staging: Three patients were in stage IV and one who had localized disease was staged as I. Due to unavailability of laboratory data only two patients with stage I were assigned with IPI score of 3 {High intermediate category).

Treatment, follow up and prognosis: Treatment details and follow up were available for two patients. Both were treated with CHOP. The follow up duration was 5 months and 14 months. After completion of first few cycles of chemotherapy both patients developed new lesions.

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA (PCMZL)

Frequency: PCMZL constitute 28% of cutaneous B cell lymphomas and 1.7% of all cutaneous lymphomas.

Age and sex: There was one 45 year old male and one 77 year old female who was affected.

Sites of involvement: The sites of involvement were trunk and head and neck region.

Clinical presentation and laboratory findings: Both patients presented with multiple nodules and respiratory symptoms of 12 months duration. Leukocytosis with lymphocytosis was present in both cases. There was mild splenomegaly in one patient. Serum LDH was moderately elevated in both cases. Bone marrow was done in one case and was not involved by lymphoma. ESR was done in one patient which was normal.

Morphology: Both cases showed nodular to diffuse dermal infiltrates sparing the epidermis. The infiltrates were composed of small lymphocytes, centrocyte like cells, lymphoplasmacytoid cells, and plasma cells, admixed with small numbers of large centroblast like cells, few eosinophils and plasma cells.

Staging: Both cases were given high international prognostic index and staged as I and IV.

Immunophenotype: The tumor cells were positive for CD20 and bcl-2. The MIB-1 proliferative index was 10-20%.

Treatment, follow up and prognosis: The treatment and follow up data were available only in the female patient. She was treated with CHOP and followed up for a period of 35 months. New lesions developed and patient deteriorated symptomatically during this period.

PRIMARY CUTANEOUS FOLLICLE CENTRE LYMPHOMA (PCFCL)

Frequency: PCFCL constitute 14% of cutaneous B lymphoma and 0.8% of all cutaneous lymphomas.

Age and sex: The patient was a fifty six year old male referred from West Bengal.

Sites of involvement: Multiple lesions developed on head and neck region for 18 months.

Clinical presentation and laboratory findings: Patient presented with multiple papules and plaques on head and neck region. He was also diagnosed to have Diabetes mellitus, Hypertension and dyslipidemia. There were no organomegaly or lymphadenopathy. There was moderate anemia and leukopenia. Serum LDH was moderately elevated. Bone marrow was involved by lymphoma.

Morphology: There was nodular dermal infiltrates with sparing of overlying hypertrophied epidermis. The infiltrate was composed of a mixture of centrocytes, relatively few centroblasts, and many lymphocytes. These atypical lymphoid cells entrapped adnexae, follicles and nerve bundles and focally extended up to the subcutaneous fat. The follicles were ill-defined and lacked tingible body macrophages. Apoptosis and mitosis were seen.

Staging: The patient presented with Stage IV with high intermediate prognostic index.

Immunophenotype: The atypical cells were positive for CD20 and MIB-1 proliferative index was 70%. CD30 and CD3 were negative. Due to unavailability of blocks additional markers were not done.

Treatment, follow up and prognosis: The patient was treated with CHOP. During therapy and follow up, he developed new lesions on scalp and chest. Subsequent biopsy showed predominant large cells with minimal number of lymphocytes, suggestive of transformation. Despite therapy symptoms worsened and patient was lost to follow up with no mentioned reasons.

?Secondary ? Metachronous lymphoma:

A 41 year old female patient from Mizoram with clinically suspected CD30 LPD presented with multiple papules and plaques on extremities since 2 months. There was associated mild lymphadenopathy and mild pleural effusion. The patient had moderate anemia. Serum LDH was moderately elevated. Bone marrow showed no involvement. The superficial and deep dermis showed perivascular infiltrates of neoplastic lymphoid cells with moderately pleomorphic nuclei, coarse nuclear chromatin and amphophilic cytoplasm. The epidermis shows hyperkeratosis, alternating orthokeratosis and parakeratosis, mild spongiosis, follicular plugging and mild flattening of rete ridges. There was no evidence of epidermotropism. On immunohistochemistry the large lymphoid cells were CD30 positive and ALK-1 negative. Predominantly CD3 positive lymphocytes were present in the background with scattered CD20 positive lymphocytes. MIB-1 labeling index was 50-60%. During evaluation of gastrointestinal symptoms, there was intraabdominal lymphadenopathy and small bowel thickening. Subsequently biopsies from both sites showed histomorphological and immunohistochemical features of diffuse large B cell lymphoma {DLBCL}. The patient was treated with multiagent chemotherapy {CHOP} as well as with localized skin treatment. The skin lesions regressed, however the GI disease persisted with involvement of descending colon during the next 12 months follow up.

RESULT OF NOTCH-1 AND FOX p1:

Total 46 blocks of 40 patients were available for Notch-1, including 23 cases of Mycosis fungoides {MF} {including 14 classical patch stage, 5 plaque stage, 2 folliculotropic MF and 2

transformed MF cases}, 4 cases of CD30 lymphoproliferative disorder {including 1 ALCL and 3 cases of LyP}, 10 cases of subcutaneous panniculitis like T cell lymphoma and 3 cases of Primary Cutaneous Gamma-Delta T cell lymphoma. Four blocks of 4 patients {2 DLBCL-leg type and 2 primary cutaneous marginal zone lymphoma (PCMZL)} were available for Fox p1. The controls, clones as well as dilution and methods are mentioned in Appendix 2&3. The proportion and intensity score were calculated and the final score was given as combination of both. The percentage of tumor cells positive for Notch1/Foxp1 was given proportion score {0: No staining, 1=<10% tumor cells, 2: 10-50%, 3: >50%} and the intensity was graded as weak, intermediate and strong and scored as 1, 2 and 3 respectively. Out of 46 blocks of T cell lymphoma, only two transformed MF cases showed positivity {both with 2+2=4 score}{See Fig.} for Notch-1 and all four B cell lymphoma cases were positive for Fox p1{ Scores for DLBCL cases were 3+3=6 and for PCMZL 3+2=5}. First two cases of B cell lymphoma showed predominantly sheet like pattern with large round cell morphology, while the other two cases showed small round cells with mild nuclear irregularity.

DISCUSSION

A total of 115 cutaneous lymphomas were diagnosed, during the 5 year period {01/05/2007 to 31/05/2012}. This comprised 2.1% {115 of 5467} of all lymphomas diagnosed during the 5 years of study which is slightly higher than documented in western literature{<1%}(2,5). The frequency of cutaneous lymphoma in our study was 1.01 per 100 biopsy specimen in contrast to 0.7 and 1.0 in Indian(30) and western literature(6). Cutaneous lymphomas comprised 9.8% of all extra nodal Non-Hodgkin's lymphomas which is similar to documented in western literature {10%}(5).

Of these cutaneous lymphomas, 89% were cutaneous T cell lymphoma {CTCL}, 6% were cutaneous B cell lymphoma and 0.9% was Blastic plasmacytoid dendritic cell neoplasm. The frequency of cutaneous T cell lymphoma was almost similar to published Indian studies {94%}(30), however study done by George et al and a documented frequency in Willemze review article were 64% and 77% respectively(6,12). The frequency of cutaneous B cell lymphoma was almost similar to previous Indian (5.67%)(30) and South East Asian studies (4%)(105). The documented frequency in western literature was higher (upto 35%)(6, 15,218), which is statistically significant {p=0.0004}. This may be due to high prevalence of Borrelia burgdorferi infection in European countries(174), which is associated with cutaneous marginal zone lymphoma. The frequency of Blastic dendritic cell neoplasm is almost similar throughout the world, however very few cases(167) have been documented with occasional case series(169).

Mycosis fungoides comprised 44 % of CTCLs and is the commonest of all cutaneous as well as cutaneous T cell lymphomas {50%}. This distribution is similar to Western, South East Asian

andIndian studies {p=0.2641}(6,105,12,13). However a study done by Doshi et al showed higher percentage of Mycosis fungoides (73%) {p=0.0001}(30). Studies done in Germany (219) and Japan (220) showed lower frequency as low as 30% due to unidentified reasons.

CLINICOPATHOLOGICAL PROFILE OF PRIMARY CUTANEOUS T-CELL LYMPHOMAS:

Age and Sex ratio: The median age of presentation was 39 years {range 3 to 88 years}. This is similar to previous published Indian, Western and South East Asian studies (6,10,12,13,30). There was a male preponderance with M:F ratio of 1.19:1, similar to reported in previous Indian, Western and South East Asian studies(12,13,30,6,10,105). Pediatric {<18 years} cutaneous lymphomas constituted 15.6%, of which mycosis fungoides {all hypo pigmented variant} was the most common (44.4%). The frequency of hypo pigmented variant in pediatric population {100%} was much higher than documented in literature {58%}(221). Frequency of overall pediatric cutaneous lymphoma is almost similar to previous Indian study {9%,}(30). Exceptionally there was preponderance of female patients in pediatric cutaneous lymphomas {M:F=0.8:1}, this is in contrast to previous Indian study(30)(M:F 2:1), a western case report(89) and a case series from Israel(221).

Sites of involvement: The most common sites of presentation were trunks and extremities {Non photo exposed areas} accounting for 56% followed by trunks, extremities, head and neck region {Photo exposed and Non photo exposed areas} 35.08% and scalp, head and neck region {Photo exposed areas alone, 8%}. The frequency of involvement was almost similar in many Indian, western and South East Asian studies (6,12,13,105). Secondary organ involvement {bone marrow} at presentation was seen in 24%, which was higher than one Korean study (4%)(105).

Clinical presentation and Laboratory findings: Macules and patches were seen in 29%, followed by nodules 28% and plaque 26% similar to what has been described in previous Indian studies (12,13) and a study by Willemze et al. There was no statistical correlation between biochemical and hematological parameters {pancytopenia, anemia, thrombocytopenia, raised LDH >1000 U/L and organomegaly} in each of the cutaneous lymphomas. There was only one study that included almost all parameters as included by us(105) and it showed almost similar findings as in our study including duration of disease.

Staging and IPI: Of available data on 49 MF cases, 80% were in stage TIA/TIB at presentation whereas the remaining 20% were in stage TII, TIII and TIV, which is similar to previous Indian and Western studies(13,93). IPI scoring was available in 41{Non MF/SS cases} cases and accordingly the risk categories were stratified as low risk in 12%, low intermediate in 68% and high intermediate in 20%. This was almost similar to a previous Indian study (13).

MYCOSIS FUNGOIDES

Frequency: Mycosis fungoides {MF} constituted 44% of all our primary cutaneous lymphomas, almost similar to the reported frequency of 45-50% in previous Indian , Western and South East Asian studies(2,6,12,13,105) though it was less than seen in studies done by Doshi et al and Saunes et al. The frequency of mycosis fungoides among all diagnosed cutaneous lymphomas was 55% in 2011 as compared to 46% in 2008. This shows the rise of mycosis fungoides, as suggested in few studies(1,7) whether due to early diagnosis with use of ancillary techniques like immunohistochemistry and TCR rearrangement or a genuine increase in number is still not known.

Age and sex ratio: A predominantly younger age group of involvement was seen in our study with a median age of 39 years, similar to previous Indian studies(13,30) but was lower than other Western or South East Asian studies {55-60 years}{p=0.0000}(6,10,105). This may be due to increased frequency of hypo-pigmented variant of MF which was more common in this age group similarly found in previous Indian studies (30,90). A definite male preponderance {M:F ratio of 1.2:1} was noted in our study, as described in different Indian, Western and South East Asian studies(6,10,12,30,105). Most of the studies have shown male predominance with a M:F ratio of approximately 2:1(6,10,30), though a similar study done in our center 4 years back by Burad et al showed a female predominance. Only 15% of our patients were less than 20 years as compared to 36% of the patients in a study by Bhuvana et al in 2000 in India. Western literature shows less than 5% of patients are less than 20 years {p=0.0000} (17). This may be due to more numbers of the Indian population being in this age group compared to the West.

Sites of presentation: The most common site of involvement was extremities and trunk seen in 57% followed by all over body including photo exposed and non-photoexposed areas seen in 17% of the patients. This was similar to previous Indian and Western literature (2,13,14). The other sites of involvement were back, chest, scalp, neck, buttocks and face, which have been documented (44,62).

Clinical presentation: In our study**,** the most common stage was the patch stage, seen in 68% followed by plaque in 29% and tumor stage seen in 9%. The frequency of patch stage was lower as compared to previous Indian study, (Burad, 86%) and other Western and South East Asian studies {85-89%} (10,44,105). The percentage of tumor stage was almost similar to Burad et

al(12%), however higher than reported by Tan et al, Ku et al and Chang et al{2.5-5%}. Majority of the cases were ISCL-EORTC stage TI/TII with 74% in stage II and the 13% in stage I; these were similar to previous studies by Burad et al, Tan et al, Anadolu et al and Van doorm et al(13,44,61,93).

Morphology: The most consistent feature in all our cases in patch stage was epidermotropism {100%} with tagging of atypical lymphoid cells along the basal layer {94%}, similar to what has been documented in Indian(13) and western literature(14,49,50). Pautrier's microabscesses were seen in 18%. The reported frequency was much higher as reported by Burad et al 50% and 37% by Ku et al -40, and Smoller et al (13,45,49). Haloed lymphocytes were seen in 64% similar to other Indian studies (13,50). Other less common features seen were pigment incontinence {21%}, edema, extravasated RBCs {5%}, colloid bodies in the epidermis {8%} and multinucleated giant cells with occasional granulomas {10%}, which have been documented in literature(2) and Indian study(13). These features were useful in differentiating Mycosis Fungoides from Pityriasis Lichenoides and other simulators. Six cases with tumor stage MF showed epidermotropism and pan dermal infiltrate of atypical lymphoid cells. Pautrier's microabscesses were seen in 1 of 6 cases. These features were similar to literature (2,13,14,43). Large cell transformation was seen in 6% which was slightly lower than studies done by Burad et al and Ku et al and Barberio et al(13,45,52).

Variants: Histomorphologically hypo pigmented variant was the most common (53 %), followed by poikilodermic{6%}, folliculotropic{4%} and one each for pagetoid reticulosis and erythrodermic MF. This was higher than documented in previous Indian

studies{p=0.1836}(30,90) and much higher than western studies{p=0.0000} (6). All pediatric MF cases were hypo-pigmented and most of them were clinically diagnosed as Vitiligo or Hansen disease as documented in literature with unusual immunophenotype (90).

Immunohistochemistry: Typical phenotype of CD3+, CD4+, CD8- and CD7-(20,43) was seen in 52% of cases. This was similar to a previous Indian study(13). A predominant CD8+ phenotype was seen 8 cases. Both CD4 and CD8 positivity is seen in one case. Large cells were CD30+ in two of the three cases with large cell transformation, similar to mentioned in standard textbooks (2,5) and previous Indian study (13). VA Nilalaou et al reported seven cases of cytotoxic CD8+ MF and showed that there was a significant difference in the clinical course of both types(56) while Willemze documented that there was no significant difference in behavior and prognosis of these cases, and these cases should not be considered separately(6). All our CD8 positive cases presented as early MF and the lesions regressed with local therapy.

SEZARY SYNDROME

There was only one case of Sézary syndrome in our study constituting 0.9% of all the primary cutaneous lymphomas, which was lower than previous Indian and Western Studies(6,12,15,30). The age of the patient was lower than reported in western literature {42 Vs. mean 60-70} (15). Our patient presented with erythrodermic skin lesions, alopecia, nail dystrophy and generalized lymphadenopathy, which is similar to what has been described in literature(6). The Sézary cell count was 6440/cumm, similar to what has been described by ISCL-EORTC definition (19). Lymph node and bone marrow were involved by lymphoma, as described in literature (2,93). Immunohistochemistry showed a CD3+, CD4+, CD8- and CD30- phenotype, similar to literature

(6,20). In our patient who presented with symptoms of erythroderma for 2 years, the classical stages of MF were not present so we included this patient in the Sézary Syndrome category and not as 'MF preceded SS', as described by Vonderheid EC et cl.(98). MUM1 was not done in our study as was done by Talpur et al.(31). Patient was treated with local therapy (PUVA) and systemic multi agent chemotherapy (CHOP) for one month, as described by Anadolu et al (93). Interferon was not included as part of his therapy. As patient was referred from Bangladesh he wanted to continue treatment at his local place. During a month of follow up, the patient didn't develop new lesions.

SUBCUTANEOUS PANNICULITIS LIKE T-CELL LYMPHOMA

Frequency: Subcutaneous panniculitis like T-cell lymphoma accounted for 21% of all our primary cutaneous lymphomas. This subtype accounts for 0.5-1% in most of the Western countries(6,219) and 10-15% in other Asian countries(10,105). This was statistically significant {p=0.0000}. A previous Indian study also showed a frequency of 15% (12,222).

Age and Sex ratio: Younger age group was affected in our study with median age of 29 years and was predominantly seen in the female population with a M:F ratio of 1:4.7. The female dominance and the similar age group has already been described in literature (2,6,13).

Sites of involvement: Most of our patients presented with subcutaneous nodules with predilection to extremities (lower limb>upper limb) and trunk, similar to what has been documented in the literature by Kong et al and Hoque et al(108,109). Bone marrow involvement was slightly higher {17%} than mentioned in previous studies (108,109).

Clinical presentation and laboratory findings: Organomegaly including hepatomegaly and splenomegaly was seen in 48% and 43% of our cases respectively. Thrombocytopenia and pancytopenia were seen in 26% and 13% respectively. Serum LDH level was elevated in 90 %. These were almost similar to what has been described in previous studies by Burad et al and Lee et al(13,28). Specifically organomegaly and lymphadenopathy were described in few studies with hemophagocytosis(6,108,109). There was no statistically significant correlation between clinical presentation and laboratory parameters with prognosis of this tumor.

Ann Arbor Staging and International Prognostic index: 86% of the patients presented with stage I/II disease suggesting localized disease and belonged to low and low intermediate risk category. This was comparable with a previous Indian study by Burad et al. in which 83% of patients presented with localized cutaneous disease and were stage I/II(13).

Morphology: All our cases had typical morphology as has been described in literature including rimming of fat spaces, hemophagocytosis and bean bag cells (2,13,108,109). Four of our patients showed granulomas with multinucleated giant cells which has been highlighted by Willemze et al and Kong et al (6,108). Bean bag cells were not significantly associated with prognosis.

Immunohistochemistry: The typical immunophenotype in our cases was CD3+ {100%}, CD8+ rimming the fat spaces {69%}, Granzyme B {88%} and CD4 (predominantly background lymphocytes} {11%}, similar to what has been documented in literature (2,6,20). CD56 was positive focally and weakly in one case, which showed deterioration of symptoms during follow up. CD56 positivity is very rare (20,107).

Prognosis and follow up: Average follow up period was 19 months in our study (range 1-80 months). Majority of the patients were treated with multiagent chemotherapy (89%). One patient showed improvement with reduction of lesions and symptomatic improvement. One patient showed angiocentricity and another angiodestruction in their biopsy. These patients showed deteriorated of symptoms as described in literature (6,108). EBV-LMP1 was not done in these cases. Both were advised TCR rearrangement study. Due to economic constraints TCR study was not done. In our study there was no statistically significant difference in prognosis related to organomegaly, hemophagocytosis or pancytopenia. These parameters were prognostically important as documented in literature (2,109). This might be due to limited follow up of our cases. Also the presence of granulomas did not show any significant correlation with prognosis or response to therapy. The significant of this is uncertain.

PRIMARY CUTANEOUS CD30 POSITIVE T-CELL LYMPHO-PROLIFERATIVE DISORDERS

There were twenty cases of cutaneous CD30 positive lymphoproliferative disorders amounting to 17% of all cutaneous lymphomas. Of these thirteen {11%} were primary cutaneous anaplastic large cell lymphoma (ALCL) and the remaining seven {6%} were Lymphomatoid papulosis (LyP).

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA {PCALCL}

PCANCL constituted 11% of all lymphomas. This was higher than the reported frequency of 8% and 2-3% in various western (6) and Indian studies (12,13,30). The median age of presentation in our study was 42 years and there was a male predominance {3:1}. The mean age of diagnosis was a decade lower than western studies (2,6) however it is comparable to previous Indian studies(13,30). Male predominance has been documented in literature and is comparable to

previous Indian (13) and western studies(6). Six of our cases had lymphadenopathy {46%} however biopsy was not performed for involvement. The literature for lymph node involvement was approximately 10% (123). The morphology and immunohistochemical features of our cases was similar to described in literature (2,6). One of our cases was positive for CD8 (7%), that was similar to what was described by Willemze et al. (5%)(6). This patient showed deterioration of symptoms during follow up. Our patients were treated with multiagent chemotherapy. Only one patient showed significant improvement (ALK positive). The prognosis of ALK positive for nodal lymphoma had already been described (223), however in skin biopsies there has not been sufficient data to establish its prognostic value. As we had only one patient who was ALk positive this is not sufficient to derive a conclusion that ALK positivity in Cutaneous ALCLs shows a better response to therapy.

LYMPHOMATOID PAPULOSIS

There were seven patients (6%) of Lymphomatoid papulosis in our study, the frequency of which was similar to an Indian study (13) but lower than reported by others (6,30)

The median age was 32 years, a decade earlier than previous Indian (30), Western and South East Asian studies(6,105). However, a study from Korea showed age of diagnosis being similar to our study(10). Most of the patients presented with localized disease in the form of papules and plaques. Majority of the cases showed a wedge shaped infiltrate with epidermotropism in one case. This is similar to what has been documented (115). All our patients belonged to the Lymphomatoid Papulosis Type A.

Immunomorphological finding in LyP in our cases was infiltrates of small to medium sized CD3+ T lymphoid cells with scattered CD30+ larger lymphoid cells. These findings are similar to what has been documented in literature (2,20). During follow up of three patients, all showed improvement with regression of lesion as has been described (115).

EXTRANODAL NK/T CELL LYMPHOMA, NASAL TYPE:

Frequency: We had only one case which was a 23 year old male which constituted 0.8% of all cutaneous lymphomas seen in our study. This patient from Andhra Pradesh was admitted with painful plaques on both legs and necrotizing lesion on the right thigh. The frequency, site and age group was similar to what has been mentioned in literature (2,6,146). The frequency of the disease is much higher in South East Asia (up to 15%) (10,105).

Clinical presentation and Laboratory findings: This patient had a short history of 8 months with organomegaly and lymphadenopathy. His bone marrow was involved at admission and LDH was elevated. Constitutional symptoms were present with ascites and splenomegaly. Anemia and leukopenia were also present. These findings were classically mentioned in a study by Lee et al and others (10,105). There was no statistically significant association between clinical parameters and laboratory investigation with prognosis of this tumor.

Morphology: There was a dense pan dermal diffuse infiltrate of atypical lymphoid cells which extended to the lobules of the subcutis as well as up to epidermis and comprised of medium to large sized cells with irregular nuclear membrane, dense chromatin and scant cytoplasm. Multinucleated and bizarre forms were present. Apoptosis and mitosis were present with

adnexal infiltration. There was no angiodestruction, in contrast to many studies in which angiodestruction was part of this neoplasm (6,105).

Immunophenotype: The atypical lymphoid cells were positive for CD3 and CD56. Cytotoxic protein TIA-1 was positive. Latent membrane protein-1 (EBV-LMP) and CD30 were negative. EBV positivity was present in majority of South East Asian patients (LEE) however in a study by Mraz-Gernhard S et al (146), the EBV positivity was seen in only 24% of cases. In our case we did not do EBER which is the gold standard for this lesion (positive in 100%) and came upon our diagnosis with clinico-pathological correlation.

Treatment, follow-up and outcome: Patient was treated with chemotherapy and radiation. Despite vigorous therapy patient died of septicemic shock one month after admission. This was similar to what has been mentioned in literature with overall survival of less than 12-15 months (105,146). Patient with extracutaneous manifestation (as in our case) survives for less than 5 months (2,6,138).

PRECURSOR HEMATOLOGIC NEOPLASM

$CD4^+/CD56^+$ HEMATODERMIC NEOPLASM

Frequency: We had only one patient, a 51 year old male which formed 0.8% of all cutaneous lymphomas in our study. This patient presented with multiple erythematous plaques over chest, back and arms similar to what has been described (2,6,138). However in contrast to studies by DiGiuseppe et al and Petrella et al(165,168), bone marrow involvement was not present.

Morphology: There was a non-epidermotropic dense diffuse pan dermal infiltrate of medium-sized mitotically active cells with finely dispersed chromatin, indistinct nucleoli and scant cytoplasm, similar to what has been described in literature (6,163,167).

Immunophenotype: The tumor cells were positive for CD4 and CD123. Few weak and faint CD56 and CD68 positive cells were present. CD3, CD20, CD30, CD7 and TdT were negative. The immunophenotype was similar to what has been mentioned in literature (20,138,167). EBV LMP1 and other cytotoxic T cell markers were not done.

Treatment and follow up: Patient was treated with systemic multiagent chemotherapy (CHOP). The patient was in clinical remission after five cycles of chemotherapy however early relapse is the rule(138,163). Our patient wanted to continue his treatment at a local hospital, so we lost him to follow up after two months.

PRIMARY CUTANEOUS GAMMA DELTA T-CELL LYMPHOMA

We had four cases of primary cutaneous gamma delta T-cell lymphoma amounting to 2.6% of all the PTCLs, similar to Western literature(6,155). Patients presented with subcutaneous nodules with ulceration. Morphology was similar to SPTCL except that involvement of superficial dermis was more commonly seen in primary cutaneous gamma delta T-cell lymphoma, similar to what has been documented in literature (6,155). All cases had a CD3+ immunophenotype with high proliferative index {75-80%}, similar to what has been documented (6,20,155). CD8 was positive in one of the three cases. Rare cases with CD8 positivity have been reported (167). TCR was done in this case, which showed clonality for gamma gene. Two cases showed hepatosplenomegaly. There were no hemophagocytosis or

angioinvasion. EBV LMP1 was not done. During follow up of two patients, these patients showed deteriorated of symptoms

PRIMARY CUTANEOUS PERIPHERAL T CELL LYMPHOMA, NOS TYPES

During review, although the diagnosis of Jessner's lymphocytic infiltrate was given in a 23 year old male, the case needs special discussion because the pattern of infiltration was unusual for Jessner's. There was no history of pruritus or burning sensation or regression of lesion, rather lesions were progressive during 12 months follow up. Based on history and histomorphological features, the lesions resembled CD 30 positive lymphoproliferative disease {LPD}, however in this case the infiltrate lacks intermixed large cells. The distribution was similar to both Jessner's infiltrate and CD30 positive LPD. The infiltrate was pan dermal which focally extended to subcutis and these cells were positive for CD3 and CD20 {CD3 slightly more than CD20}. The involvement of active lesion in non photoexposed areas also favored a diagnosis of Jessner's infiltrate though polymorphous light eruption or Discoid lupus erythematous could not be excluded. Due to unavailability of blocks {for other ICC}, follow up data and detailed clinical history, this case was included in PTCL- NOS category.

We had one case of intravascular T cell lymphoma which also needs special mention as most cases of intravascular large cell lymphoma are of B cell phenotype. Very few cases have been described with intravascular T/NK cell phenotype(224). Our patient was younger (43 year old) than reported in literature (224). The sites of involvement were almost similar to what is described in literature (224). In our case cytotoxic markers were noncontributory and CD56 was equivocal. EBV LMP1 was not done. T cell rearrangement was not done due to economic

constraints. Based on available markers this case can be categorized into PTCL- NOS subtype probably intravascular peripheral T cell lymphoma. The patient died within two months of diagnosis and multiagent chemotherapy a fate similar to what has been described in a small set of cases by Cerroni et al. There have been case reports of these lymphomas with no progression of disease; even though the lesions were refractory to combination and salvage chemotherapy (225).

One of our patients showed dermal histiocytic infiltrate and associated helper T cell immunophenotype. There were increased numbers of foamy histiocytes as well as eosinophils. There are limited available data for atypical lymphohistiocytic infiltrates involving dermis(226). Other infective etiologies were ruled out by special studies as well as correlating with laboratory parameters. The elevated MIB-1 proliferative index {50%} raised the suspicion of the neoplastic nature of this condition. Based on clinical and immunophenotyping features this case may be fitted into atypical histiocytic lesion of skin. As blocks were not available, additional studies were not possible (CD 163). TCR rearrangement study was not done. The patient was lost to follow up after two months due to unknown reasons.

Primary cutaneous T lymphoblastic lymphoma of skin is rarely reported in literature(227). However this could also be early manifestation of systemic acute lymphoblastic leukemia (ALL)(228). As we didn't have history or other laboratory parameters for our patient we do not know if this T ALL was primary or secondarily involving the skin due to dissemination as has been described by Millot et al(228). The lesions may manifest before the diagnosis of

hematological disease {from 8 days upto 6 months}(228). The site of involvement {head} was also similar to what has been described in literature (228).

CUTANEOUS B CELL LYMPHOMAS

FREQUENCY OF SUBTYPES OF CUTANEOUS B CELL LYMPHOMAS:

Cutaneous B cell lymphomas comprised 6% of all cutaneous lymphomas similar to studies by Doshi et al, Lee et al and Nagasawa et al (5.67%, 4%, 12 %) (30,220) but was lower than other studies by George and Willemze et al (22.5% and 18.8%) (6,12). This may be due to increase number of indolent B cell lymphoma found in European countries and increased incidence of Borrelia infection in Europe.

Diffuse large B cell lymphoma (DLBCL) was the most common subtype of all cutaneous B cell lymphomas comprising 57%, followed by primary cutaneous marginal zone lymphoma (PCMZL) which was 28%. DLBCL and PCMZL constituted 3% and 1.7% of all cutaneous lymphomas respectively. The detailed sub classification of PCBCL is not mentioned in any of the previous Indian studies. The major studies done by Senff (N=300) and Willemze (N=317) have classified B cell lymphomas into primary cutaneous follicle center lymphoma(PCFCL), primary cutaneous marginal zone lymphoma(PCMZL) and primary cutaneous large B cell lymphoma-leg type(6,16).

Age and Sex ratio:

The mean age of presentation was 55 years {Range 42-77 years} with a M:F ratio of 2.5:1. This was similar to studies published by Doshi et al published with age range of 41-60 years and sex

ratio of 3:1(30). Another study done on 300 cutaneous B lymphomas showed a mean age of 62 years with M: F ratio of 1.4:1(16).

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA {PCMZL}

Frequency: PCMZL constitute 28% of cutaneous B cell lymphomas and 1.7% and all cutaneous lymphomas similar to what has been documented by Senff and Willemze et al (6,16). In our study there were 2 patients (one male and one female) aged 45 years and 77 years respectively where we had a 1:1 ratio. Other studies have specified a male predominance(6,16).

Clinical Presentation and Morphology: Both of our patients showed multiple nodular lesions over trunk and extremities. On histomorphological examination both cases showed infiltrates composed of small lymphocytes, centrocyte like cells, lymphoplasmacytoid cells, and plasma cells, admixed with small numbers of large centroblast like cells as described by Senff, Willemze and Rijlaarsdam et al (6,16,195). None of the cases were associated with Borrelia infection or autoimmune disorder as mentioned in literature(174,176). There were neither organomegaly nor peripheral lymphadenopathy. Bone marrow was not involved in any of the cases. There was no significant correlation between clinical presentation and laboratory parameters with prognosis of this tumor.

Immunophenotype: The neoplastic cells were positive for CD20 and bcl-2. The MIB1 proliferation index was low. This was similar to study documented by Laurence et al(179).

Treatment and follow up: Follow up was available only in one patient for 35 months. She was treated with multiagent chemotherapy. She developed new lesions but showed mild

symptomatic improvement. However other studies have showed 100% survival with good prognosis(6,16,170).

PRIMARY CUTANEOUS FOLLICLE CENTRE CELL LYMPHOMA (PCFCL)

Frequency: Only one patient was present in our study which constituted 14% of all cutaneous B cell lymphoma and 0.8% of all cutaneous lymphomas. This was much lower than the published western studies, in which it constituted 50% of cutaneous B cell lymphomas(6,16).

Age/Sex and Presentation: Our patient was a 56 year old male with multiple papules and plaques over head and neck region for the last 18 months, similar to what has been described by Senff and Willemze et al(6,16). There was no organomegaly or significant peripheral lymphadenopathy {sub centimetric cervical lymph node, not biopsied} on presentation.

Morphology: There was a non epidermotropic nodular dermal infiltrate of centrocytes admixed with few centroblasts and many lymphocytes sparing the overlying epidermis. This was similar to studies done by De Leval et al and Senff et al.(6,179) . A follicular pattern is more commonly observed in the scalp region than those arising from trunk(6).

Immunophenotype: These atypical cells were positive for CD20 with MIB-1 proliferative index of 40%(6,185). Bcl-6, Bcl-2 and CD 10 were not done.

Treatment, follow up and prognosis: The patient was treated with multiagent chemotherapy; however the lesions progressed with development of new large lesions. Follow up biopsy showed large cell transformation with bone marrow involvement. The documented survival in this lymphoma was over 95%(6,16,185). But there were studies that extracutaneous

progression of this lymphoma may be seen in upto 10.5% of cases(16). That could be better explained in our case. Furthermore presence of Bcl-2 positivity with diffuse large cell histology may be helpful in predicting the prognosis(16). In our case, there were not many large cells and Bcl-2 was not done due to classic morphology.

PRIMARY CUTANEOUS DIFFUSE LARGE B CELL LYMPHOMA, LEG TYPE

Frequency: PCLBCLconstituted 57% of cutaneous B cell lymphomas and 3% of all cutaneous lymphomas respectively. There were no published Indian studies on subcategorisation for this lymphoma group. A similar result was obtained in studies done by Willemze, Lee, Nagasawa et al(6,105,220). A study done on 300 cutaneous B lymphomas by Senff et al showed 19% of patients had PCBCL-leg type (16).

Age, Sex and Presentation: There were four patients included in our study where mean age of diagnosis was 52 years with M:Fratio of 3:1. The common sites of involvement were extremities, trunk and lower back. This was similar to Indian (30), Western and South East Asian studies(6,16,105). Female preponderance was documented in PCDLBCL-leg type(6,16).

Clinical presentation and morphology: All patients presented with multiple nodules over trunk and extremities. The atypical infiltrate involved dermis without epidermotropism and in two cases it infiltrated adnexa. Mitosis and apoptosis were increased. This is similar to what has been described in literature(2,6,16). Two of our patients presented with organomegaly and lymphadenopathy {not biopsied}. One patient had anemia. There was no pancytopenia. All cases showed diffuse CD20 positivity. Bcl-6 was done in one case, which showed positivity for atypical cells. The average MIB-1 proliferation index was 75%. There was no statistically

significant correlation between clinical presentation and laboratory parameters with prognosis of this tumor.

Staging, treatment and follow up: Majority of the patients presented with stage III disease. Two patients were treated with multiagent chemotherapy (CHOP) however there was no improvement in any of the patients. As described by Senff and Grange et al, multiple skin lesions, round cell morphology and location on the leg were the most important poor prognostic factors(16,194). In all our cases there was more or less round cell morphology, multiple skin lesions and two patients with leg involvement as part of systemic disease. Follow up data of two patients were available and both showed deterioration of symptoms {mean follow up duration -10 months}.

Development of secondary malignancy had already been discussed with Mycosis Fungoides. However in our case we had a CD30 positive lymphoproliferative disorder {CD20 negative} and concomitant nodal/GI {Gastrointestinal} diffuse large B cell lymphoma. This was an unusual and rare event. It is not clear whether they originate from the same precursors or both arise with different de novo pathogenesis. After extensive literature review we could not decide whether this was aberrant CD30 positivity in a DLBCL as has been described or 2 different tumors being seen simultaneously like a Metachronous tumor.

RESULT OF NOTCH-1 AND FOX P1:

Notch 1 and Fox P1 were done. The former on T cell lymphomas and the latter on B cell lymphomas. Only two transformed MF cases showed weak positivity for Notch-1 {2 of 40 cases}, this was lower than what has been described by Kamstrup et al {p=0.0000}(216). Also,

none of the CD30 positive lymphoproliferative disorder cases {4 cases} showed positivity for Notch=1, as described by the same author(215). This could be either because the blocks taken were old and antigenicity had decreased or the life span of the antibody vial was very low. Due to financial constraints we were unable to redo the negative cases. Four blocks from 4 patients with cutaneous B cell lymphomas {2 DLBCL and 2 PCMZL} were available for Fox p1 study. All showed diffuse and intense Fox p1 positivity {Score 3+3=6} similar to what has been described by Senff(16).

SUMMARY AND CONCLUSION

1. The frequency of cutaneous lymphoma in our five year study was 1.01 per 100 biopsy specimens; this was almost similar to the frequency documented in Indian and western literature.

2. Cutaneous lymphomas comprised 9.8% of all extra nodal Non-Hodgkin's lymphomas and 2.1% of both nodal and extra nodal lymphomas, similar to that documented in Indian and western literature. The frequency of cutaneous T cell lymphoma was lower than previous Indian and Western studies. The frequency of cutaneous B cell lymphoma was almost similar to previous Indian and South East Asian studies and much lower than what has been documented in Western literature. This was statistically significant {p=0.0004}.

3. The frequency of Mycosis fungoides was similar to that in Western literature and lower than previous Indian studies. The frequency of mycosis fungoides among all diagnosed cutaneous lymphomas was 46% in 2008 as compared to 55% in 2011. This indicates a rising trend in mycosis fungoides, as suggested by Western studies. This could be due to early diagnosis, more use of immunohistochemistry and TCR rearrangement studies. There was preponderance of female patients in pediatric cutaneous lymphomas. This was in contrast to a previous Indian study and a case series done in Israel. A predominantly younger age group of involvement was seen in our study for Mycosis Fungoides with a median age of 39 years, similar to previous Indian studies. Age at presentation and diagnosis was lower than other Western and South East Asian studies significantly {p=0.0000}. In our study only 15% of patients were less than 20 years of age

as compared to 36% in a previous Indian study. This is in contrast to western literature where lymphomas in patients < 20 years were less than 5%. This was statistically significant {p=0.0000}. Histomorphologically hypopigmented variant was the most common of all Mycosis Fungoides variants comprising 53%, which is higher than documented in previous Indian studies{p=0.1836} and much higher than the Western literature{p=0.0000}. All pediatric Mycosis Fungoides cases were hypopigmented and most of them were clinically diagnosed as Vitiligo or Hansen disease as documented in literature with unusual immunophenotype{CD4/CD8 positive or CD8 positive} and associated with good prognosis.

4. Subcutaneous panniculitis like T-cell lymphoma accounted for 21% of all our primary cutaneous lymphomas, significantly higher than reported in western literature and almost similar to previous Indian and Far East Asian studies. This was statistically significant{p=0.0001} Bone marrow involvement in subcutaneous panniculitis like T cell lymphoma was slightly higher {17%} than documented in other Indian and Far East Asian studies. One out of two CD56 positive cases showed significant deterioration of symptoms. As there was only one case, this finding cannot be used to prognosticate authoritatively. There was no prognostically significant difference in prognosis if there was associated hemophagocytosis syndrome or hepatosplenomegaly as has been reported by other studies.

5. The frequency of primary cutaneous anaplastic large cell lymphoma was higherthan Western and Indian studies. The mean age of diagnosis of primary cutaneous anaplastic

large cell lymphoma {PCALCL} was a decade lower than in Western studies and it was comparable to previous Indian studies. Only one patient of PCALCL showed significant improvement {ALK positive}. The good prognosis of ALK positive nodal and extra nodal cutaneous anaplastic large cell lymphoma has already been documented.

6. The frequency of Lymphomatoid papulosis was lower than what has been documented in previous Indian and Western studies. The median age of Lymphomatoid papulosis was 32 years, a decade lower than previous Indian and Western/Far East studies. We had only type A LyP in our study with no type B, C, D or E. Their prognosis was or was not influenced by B symptoms, epidermal ulceration, lesions in photo exposed and non photoexposed areas, number of CD30 + cells present and type of associated infiltrate present.

7. A case of extra nodal NK/T cell lymphoma, nasal type was present in our study. The frequency of this lymphoma was much higher in Far East Asian studies (up to 15%). This was statistically significant. Despite vigorous therapy the patient with extra nodal NK/T cell lymphoma, nasal type died of disease after one month of admission. This was similar to previous literature with an overall survival of less than 12-15 months. Because of extracutaneous dissemination the patient died within a short duration, as has been documented in a study where the survival was as low as five months.

8. There was only one case of Blastic dendritic cell neoplasm during the study period. The documented frequency was almost similar. However, bone marrow involvement was not present, which was the most consistent finding in previous studies. The patient was

in clinical remission after five cycles of chemotherapy. As the patient wanted to continue his treatment at a local hospital, we lost him to follow up after two months.

9. We had four cases of primary cutaneous gamma delta T-cell lymphoma amounting to 2.6% of all the cutaneous lymphomas, similar to Western literature. These were empirically diagnosed based on clinico-pathological correlation. TCR rearrangement was done only on one of these cases which showed positivity. Gamma delta immunohistochemistry was not done on these cases. All these patients did not fare well and deteriorated after 6 months.

10. In the absence of history and peripheral smear data, the “primary” cutaneous T lymphoblastic lymphoma of skin is worthy of mention as a unique case. Only follow up data of this patient will definitely be able to identify this case as primary or secondary as ALL is known to present as cutaneous lymphoma 8 months to 2 years prior to its appearance in the bone marrow.

11. There were totally 3 patients in our study who died of cutaneous lymphoma. One had extra nodal NK-T cell lymphoma, another had Mycosis Fungoides in Transformation and the third had PTCL- NOS empirically classified into Intravascular T cell lymphoma. The survival of all these patients was less than 10 months, as documented in previous studies.

12. In contrast to western literature, primary cutaneous diffuse large B cell lymphoma, leg type was the most common subtype of all cutaneous B cell lymphomas in our study {4 of 7 cases}. The patient of primary cutaneous follicle center lymphoma was treated with

multiagent chemotherapy; however the lesions progressed with development of new large lesions showing large cell transformation. The documented survival in this lymphoma was over 95%. But there was a study that documented extracutaneous progression of this lymphoma might be seen in upto 10.5%. This was illustrated in our case. Majority of the primary cutaneous diffuse large B cell lymphoma, other cases presented with stage III with deterioration of symptoms during follow up.

13. “Metachronous” lymphoma {CD30 positive lymphoproliferative disorder and diffuse large B cell lymphoma of GI tract} whether it was a DLBCL with aberrant CD30 positivity in the skin or truly a Metachronous lymphoma is something we do not know.

14. The result of Notch-1 immunocytochemistry for cutaneous T cell lymphoma was lower than mentioned in a study by Kamstrup et al. However it was significant in our study {p=0.0000}. The cases of CD30 lymphoproliferative disorders were also negative for Notch-1 as compared to a published study by the same author. However the overall data on Notch-1 was limited for comparison and to arrive at a definite conclusion.

15. The result of Fox p1 was comparable to a previous documented study. The round cell morphology and diffuse pattern were associated with worse prognosis which was what we saw in our study as well though the number of cases were few.

Limitations of the Study:

Due to financial constraints we were unable to do TCR rearrangement on the lymphomas when applicable. Markers like gamma delta, Beta F1 were not available when the original diagnosis was made and more money was needed for new markers. Also for prognostication Notch 1 and Fox P1 look a long time and material to standardize and hence more antibody was needed than originally estimated for the total number of cases on which it was done.

Conclusions:

Cutaneous lymphomas though it forms only around 10% of the total extra nodal lymphomas are challenging for their versatile presentation. Classification of these lymphomas has undergone a sea change since the 1980s with new entities being added on with each WHO edition that comes into print. Also knowledge of entities like Indolent CD8 positive T cell lymphoma of the ear and CD8 positive aggressive epidermotropic cytotoxic T cell lymphoma will help in differentiating it from Mycosis fungoides, Pityriaris Lichenoides Chronica, Vitiligo by clinico-pathological correlation only and not by histology or clinical features alone.

Diagnosis of each entity represents a challenge as it is different from its nodal counterpart or does not have a nodal counterpart. Most of the cutaneous T cell lymphomas have good prognosis with respect to their nodal counterparts. FOXP1 and Notch 1 can be used in the future for prognostication of these lymphomas and new markers like Beta F1 and Gamma delta and EBER done on a routine basis will also help in making diagnosis easier.

ILLUSTRATIONS

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF EARLY MYCOSIS FUNGOIDES.

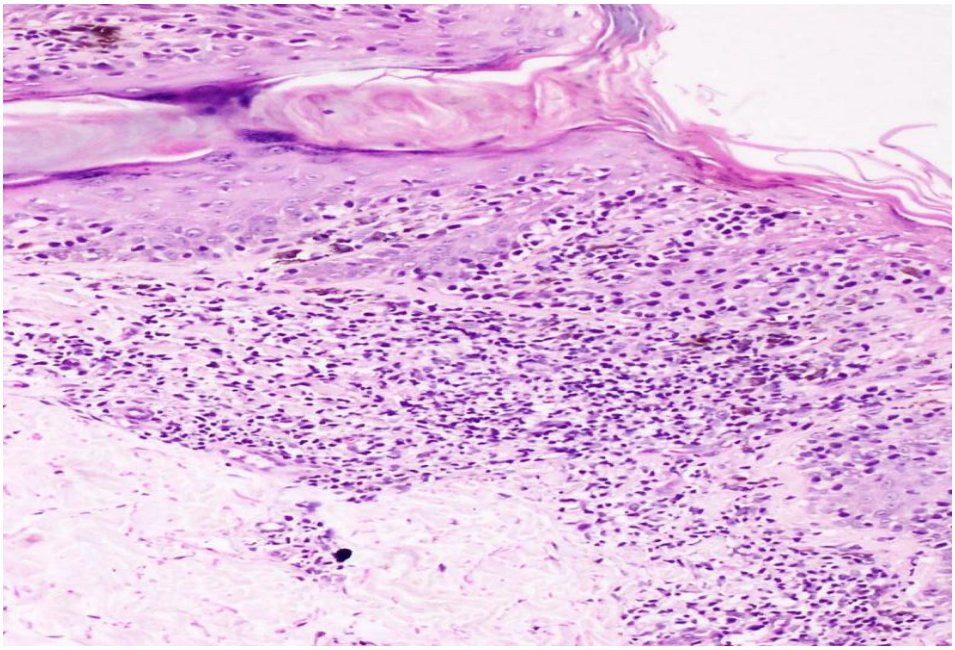


Figure 1: Early Mycosis Fungoides: Shows tagging of lymphocytes with string of beads appearance H&E 100X

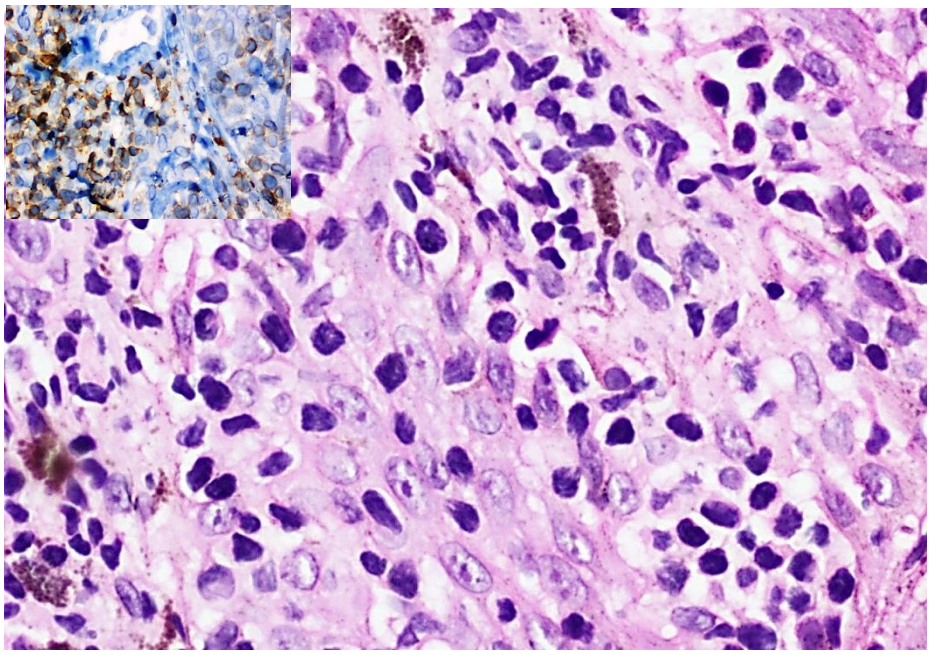


Figure 2: Early Mycosis Fungoides: Shows atypical small to medium sized cells with hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm {H&E 400x}. Inset picture shows the tumor cells are positive for CD3 {also CD4 positive-NOT SHOWN}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF HYPOPIGMENTED MYCOSIS FUNGOIDES {CD 8+VE}.

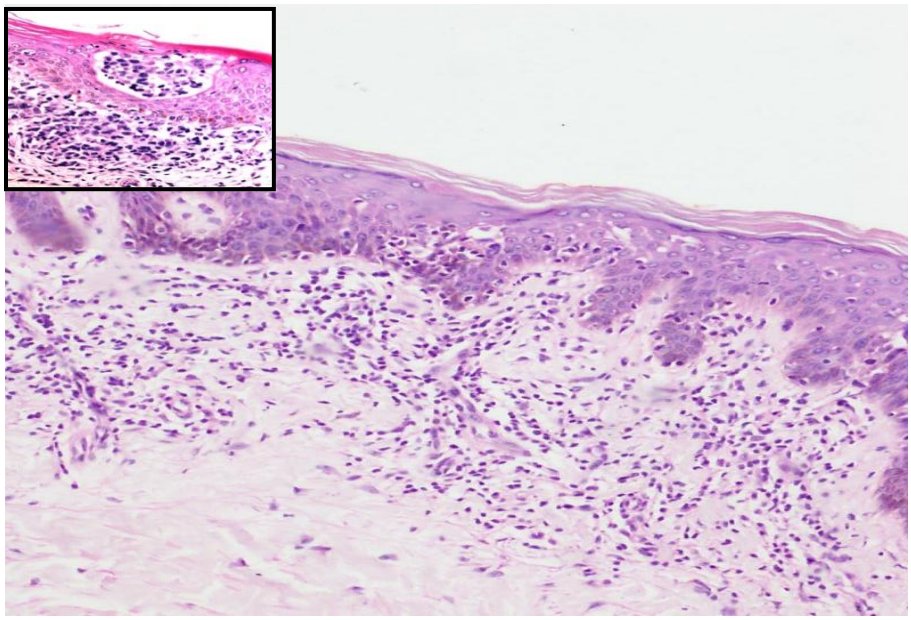


Figure 3: Hypopigmented Variant of Mycosis Fungoides: Shows atypical lymphoid infiltrate showing epidermotropism trying to form Pautrier's micro abscess {Inset, top left}. H&E 100x

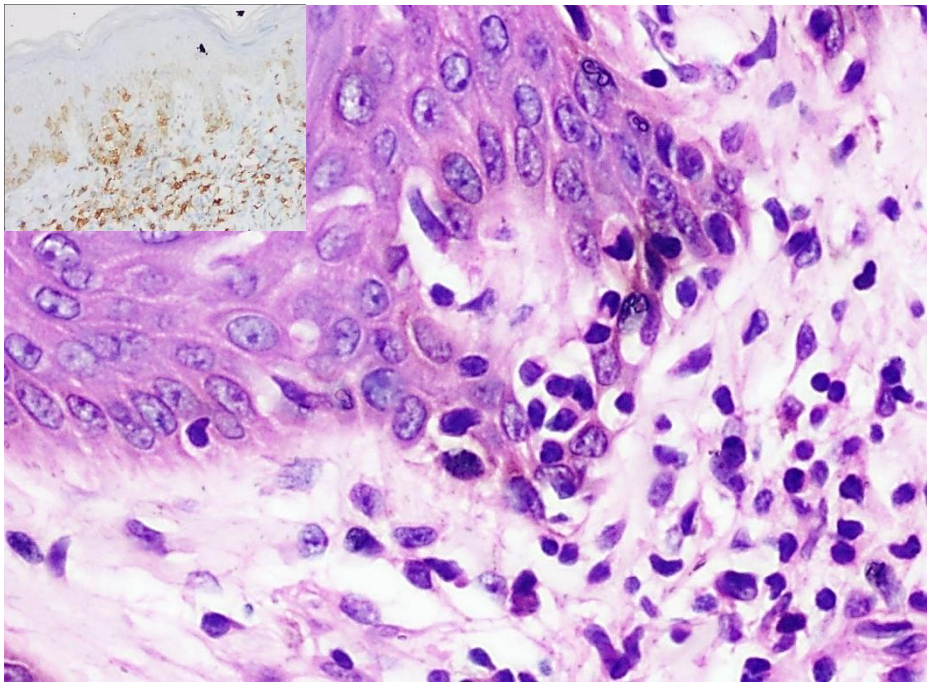


Figure 4: Hypopigmented Variant of Mycosis Fungoides: Shows the atypical infiltrate showing epidermotropism with medium sized round to oval nuclei, inconspicuous nucleoli and scant cytoplasm {H&E 400x }. Inset picture shows the tumor cells are positive for CD3 {not shown} & CD8 {top left}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF JUVENILE HYPOPIGMENTED MYCOSIS FUNGOIDES{CD 8+VE}.

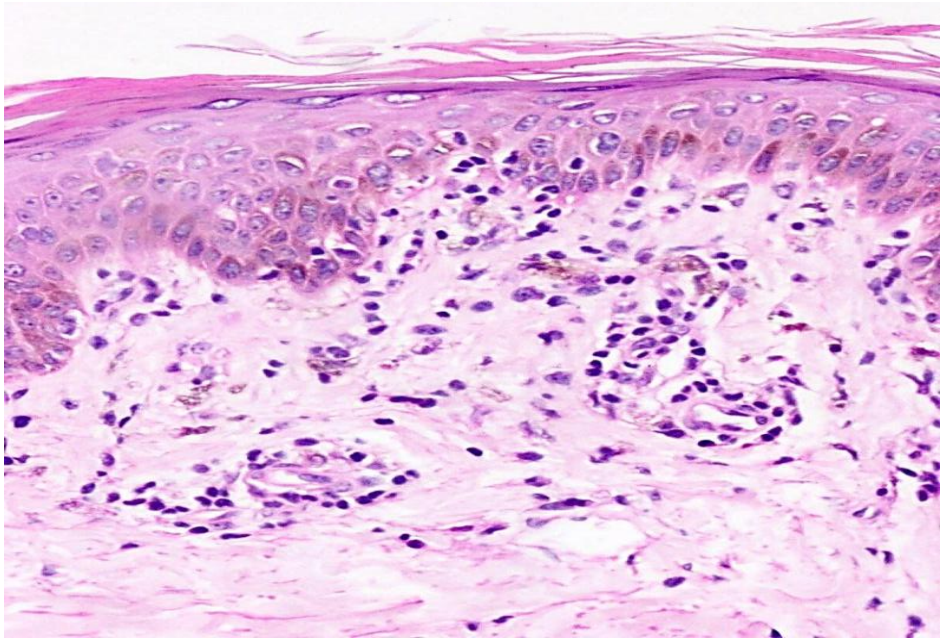


Figure 5: Juvenile hypopigmented Mycosis Fungoides: Shows atypical infiltrate reaching upto epidermis with dermo-epidermal tagging and focal epidermotropism. H&E 200x

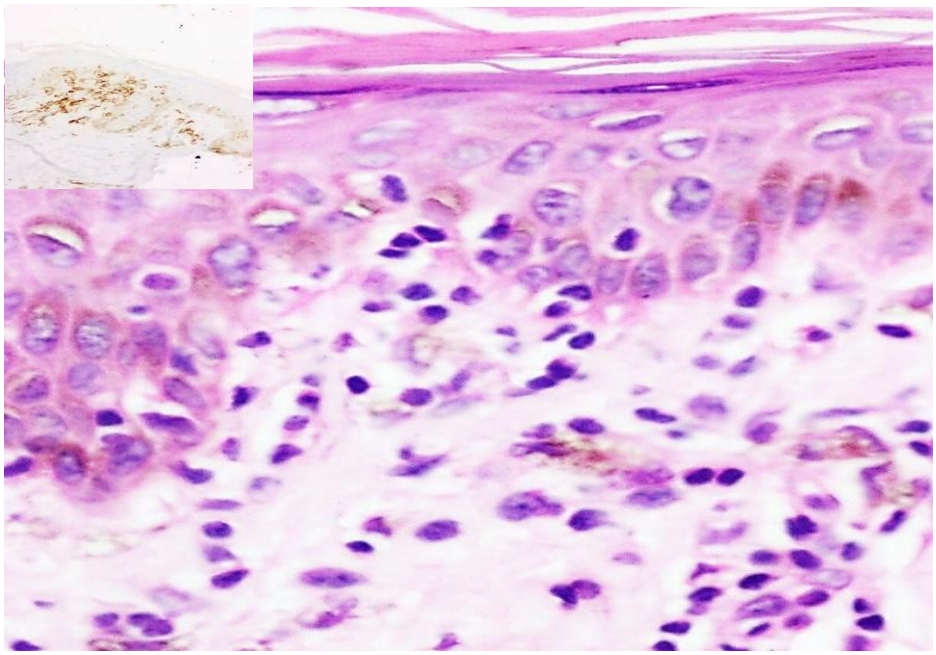


Figure 6: Juvenile hypopigmented Mycosis Fungoides: Shows atypical lymphocytes with perinuclear halo and focally interepidermal aggregates without spongiosis{ H&E 400x}. The tumor cells are positive for CD3{not shown} and CD8{top left-inset picture}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF FOLLICULOTROPIC MYCOSIS FUNGOIDES.

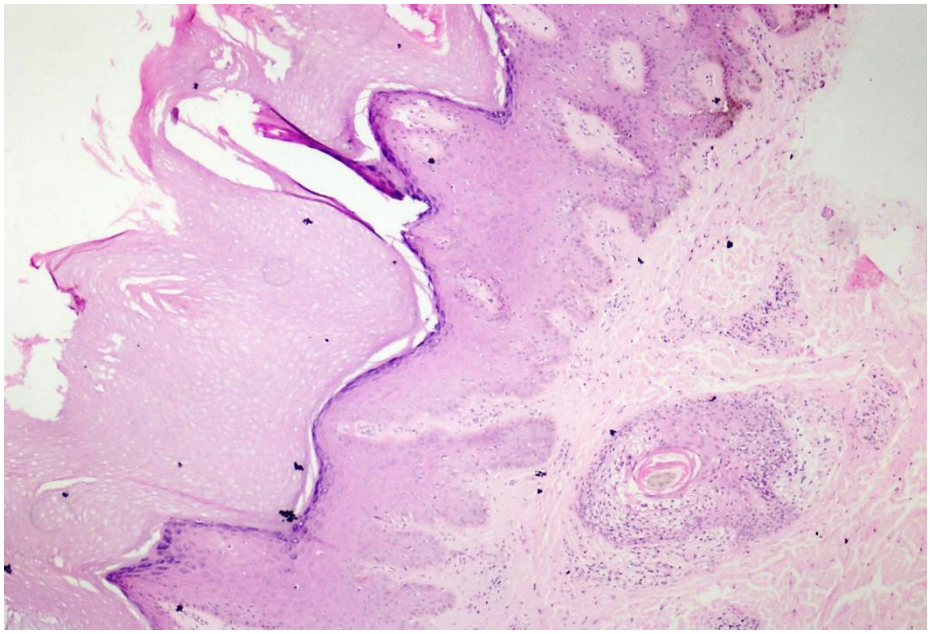


Figure 7: Folliculotropic MF: Shows perifollciular edema with mild to moderate infilrates associated with epidermal irregular acanthosis and compact marked hyperkeratosis. H&E 40x

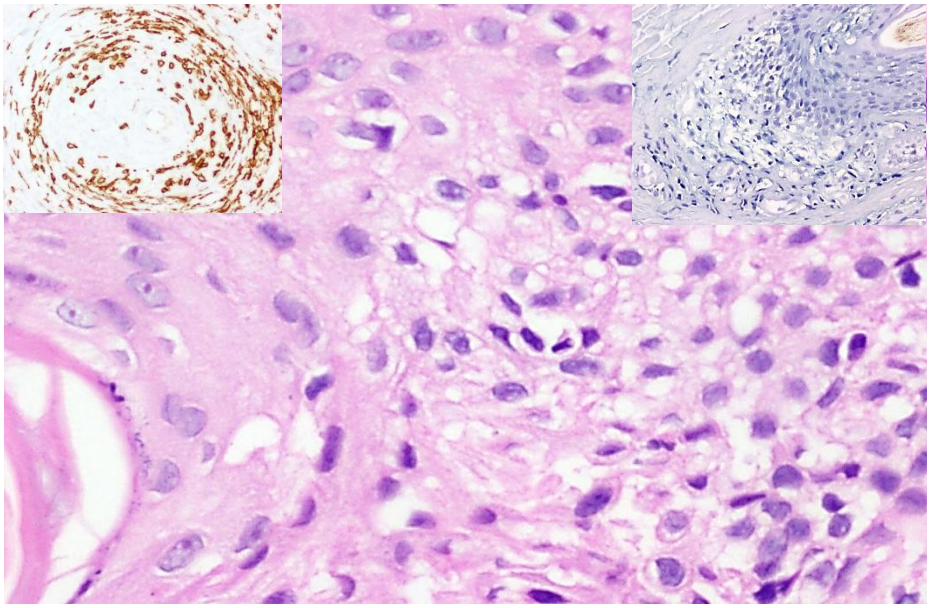


Figure 8: Folliculotropic Mycosis Fungoides: Shows follicular keratinocytes infiltrates by atypical keratinocytes with focal epidermotropism forming small aggregates. These cells are hyperchromatic with inconspicuous nucleoli and scant cytoplasm{H&E 400x}. The atypical infiltrates are positive for CD3{inset top left}, CD4{not shown} with increase in intrafollicular mucin{colloidal iron, top right}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF POIKILODERMIC MYCOSIS FUNGOIDES.

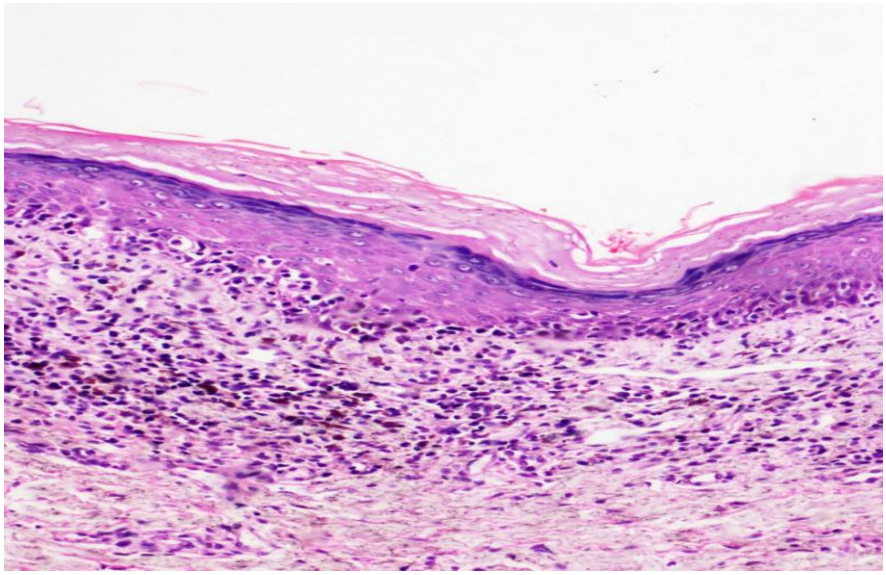


Figure 9: Poikilodermic Mycosis Fungoides: Shows atypical lymphoid infiltrate tagged at dermo-epidermal junction with dermal pigment incontinence. H&E 100x

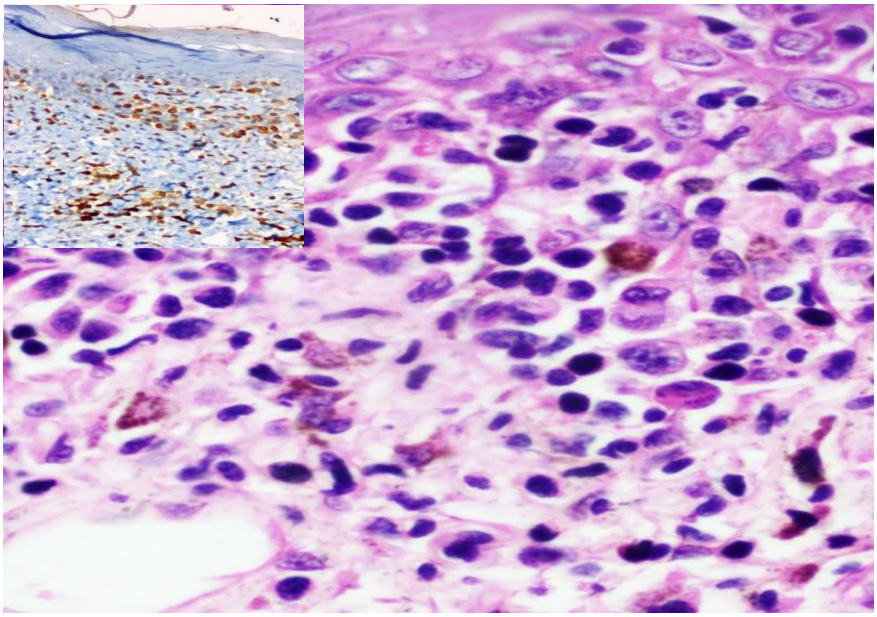


Figure 10: Poikilodermic Mycosis Fungoides: Shows infiltrate consists of small to medium sized atypical cells with hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm{H&E 400x}. Inset picture shows the tumor cells are positve for CD4{top left}{also positive for CD3-NOT SHOWN here}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF MYCOSIS FUNGOIDES IN TRANSFORMATION.

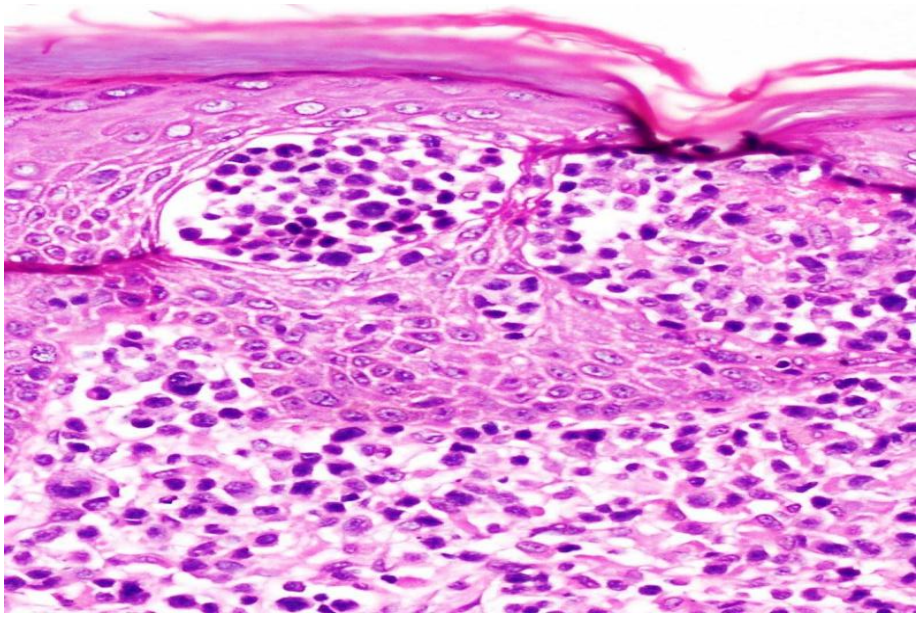


Figure 11: Mycosis Fungoides in Transformation: Shows atypical lymphoid infiltrates mixed with other inflammatory cells. This cells are collected in artefactual space created within epidermis. There is no convincing epidermotropism. H&E 100x

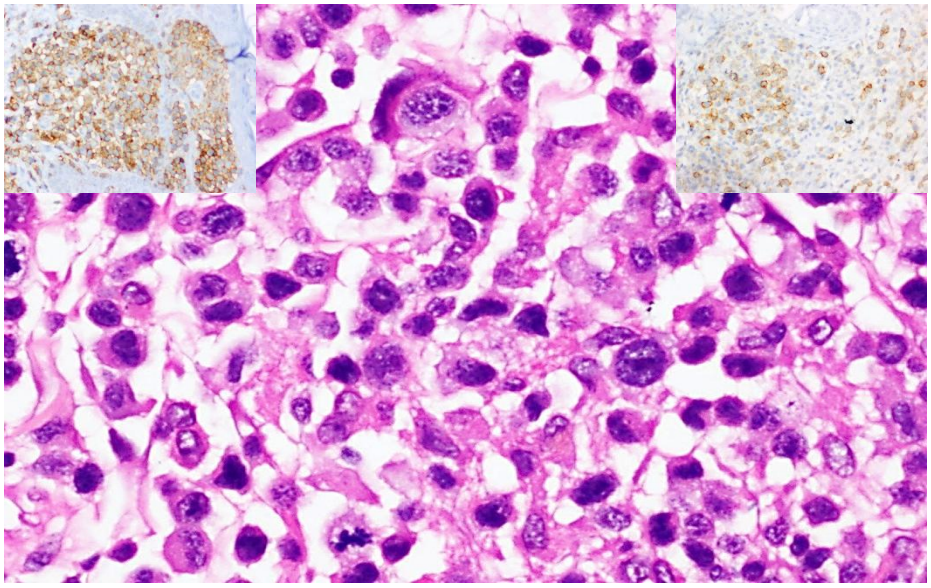


Figure 12: The atypical infiltrate comprised of predominantly medium to large cells with hyperchromatic to coarse chrmatin, inconspicuous nucleoli and scant to moderate amoutns of cytoplasm { H&E 400x}. The atypical infiltrates are positive for CD4{inset-top left, CD30{large cells, top right} and negative for CD7{not shown}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF SEZARY SYNDROME.

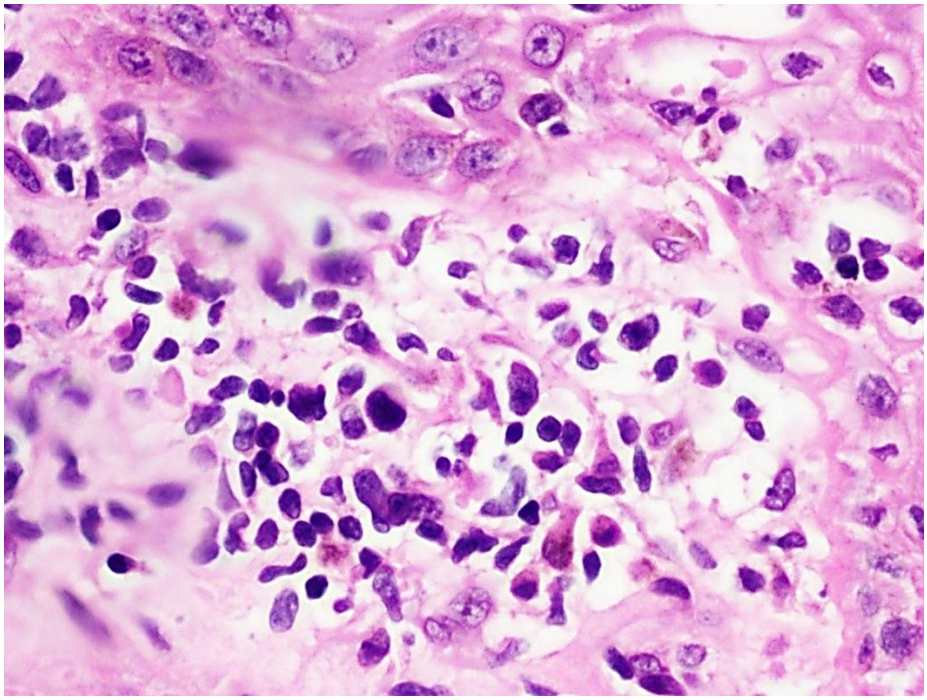


Figure 13: Sézary syndrome: The atypical lymphoid infiltrates shows epidermotropism with perinuclear halo with spongiosis of epidermis leading to formation of vesicles. H&E 100x

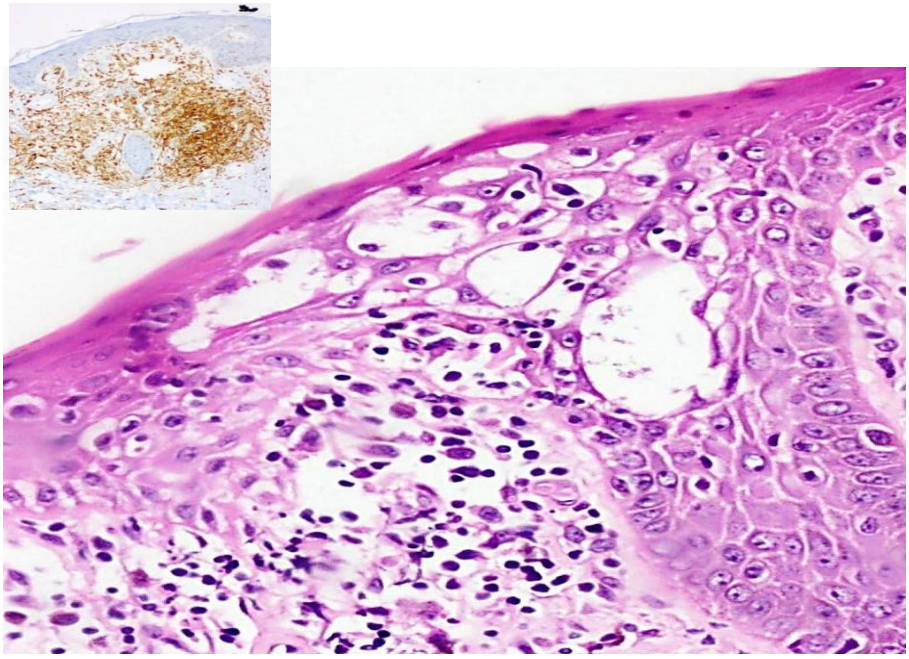


Figure 14: Sézary syndrome: The atypical lymphoid infiltrates show epidermotropism, tagging, perinuclear halo and hyperchromasia. Note: There is no other inflammatory infiltrate in epidermis {H&E 400x}. The atypical lymphoid cells are positive for CD3{top left}, CD4{not shown} and negative for CD7{not shown}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS CD30 POSITIVE LYMPHOPROLIFERATIVE DISORDER.

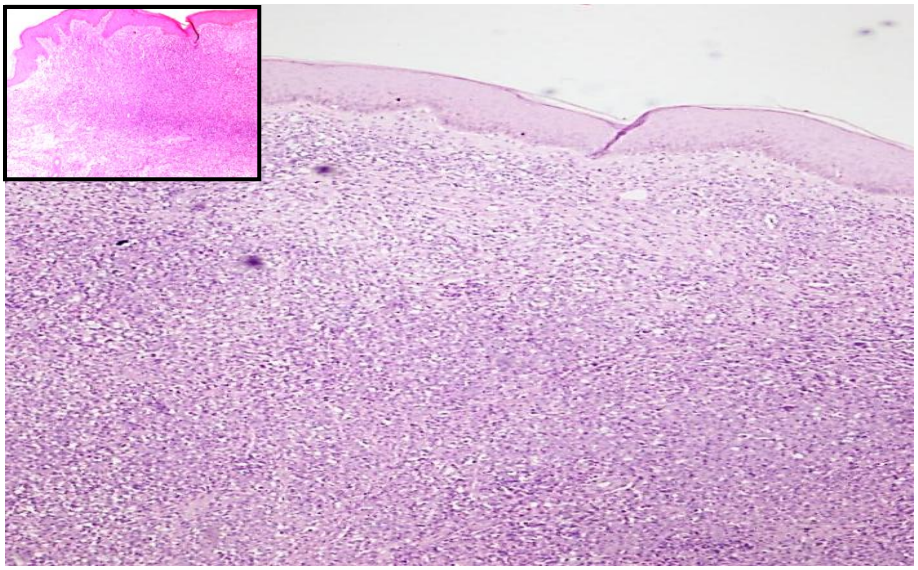


Figure 15: Primary cutaneous CD30 positive lymphoproliferative disorder: Shows tumor in the dermis with few large pleomorphic cells visible at this power also. Note that there is grenz zone between tumor and epidermis {Inset top left: wedge shaped infiltrate in Lymphomatoid papulosis}.H&E 40x

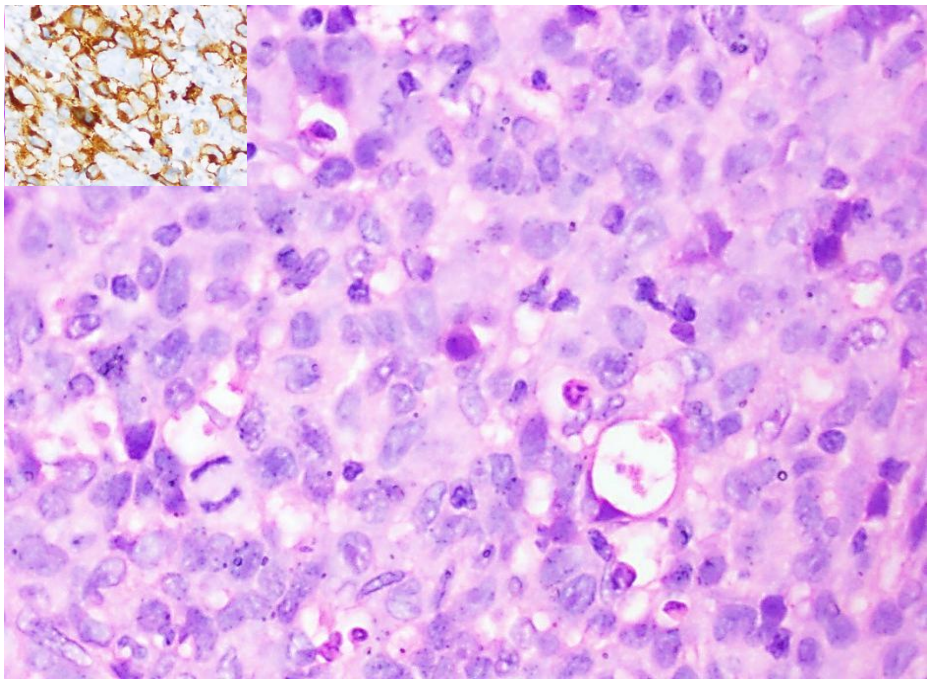


Figure 16:Primary cutaneous CD30 positive lymphoproliferative disorder: Sheets of large cells with moderate to marked pleomorphism including mitotic figures and few large pleomorphic cells {H&E 400x }. Inset {on top left} picture shows these large cells are positive for CD 30.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF SUBCUTANEOUS PANNICULITIS LIKE T CELL LYMPHOMA.

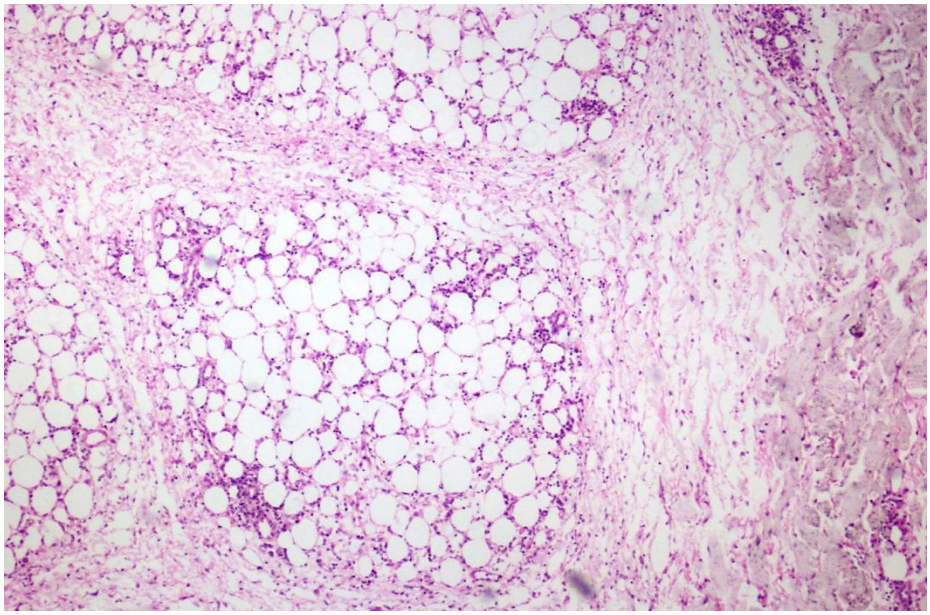


Figure 17: Subcutaneous panniculitis like T cell lymphoma: Shows diffuse infiltrates involving predominantly lobules of subcutis. H&E 40x

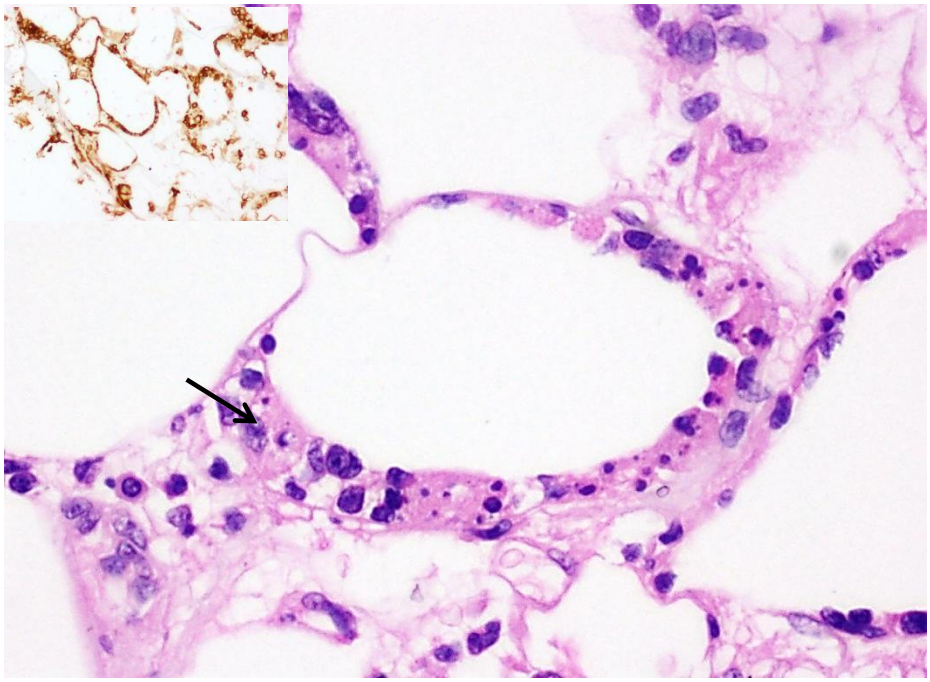


Figure 18: Subcutaneous panniculitis like T cell lymphoma: Shows rimming of adipocytes with few histiocytes engulfing nuclear dust forming bean bag cells{arrow}{H&E 400x}. The atypical lymphoid cells are positive for CD3{not shown} and CD8{top left}.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS EXTRA NODAL NK/T CELL LYMPHOMA, NASAL TYPE.

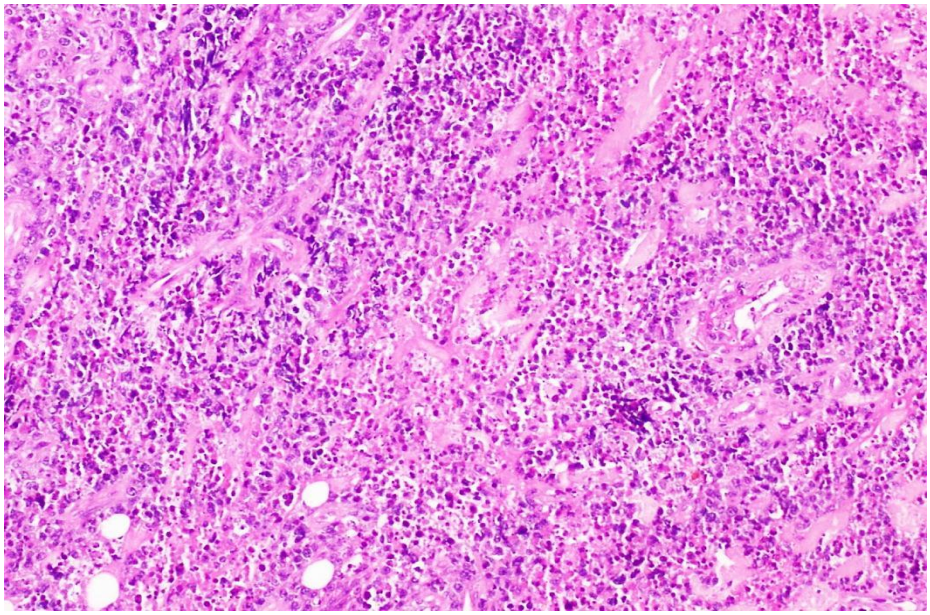


Figure 19: Primary cutaneous extra nodal NK/T cell lymphoma, nasal type: Shows dermal perivascular and interstitial infiltrates of atypical cells with vascular proliferation. H&E 100x.

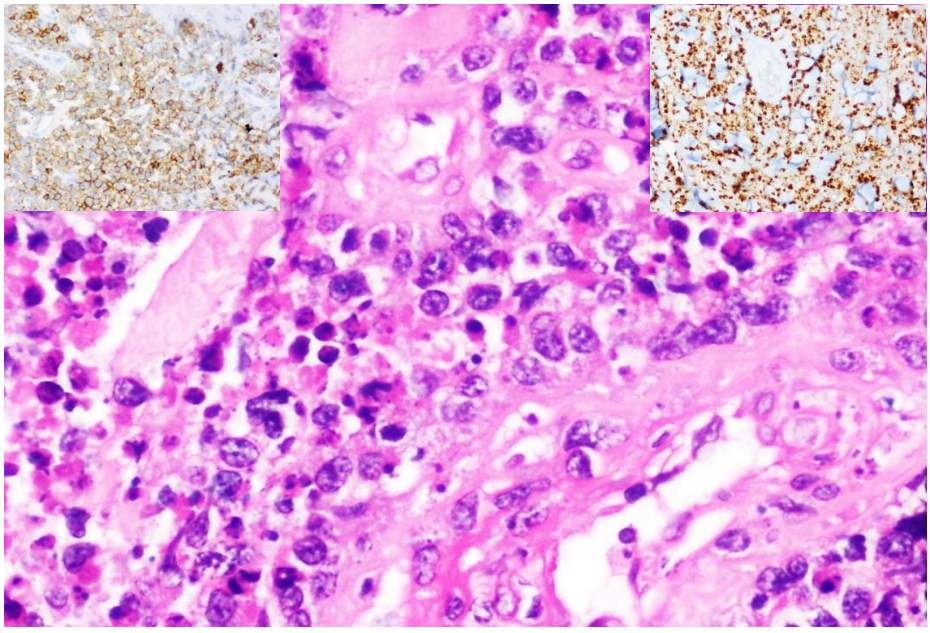


Figure 20: Primary cutaneous extra nodal NK/T cell lymphoma, nasal type: Shows medium sized atypical lymphoid cells with round to oval nuclei, coarse chromatin, mild nuclear irregularity, and scant cytoplasm {H&E 400x}. Inset pictures show the tumor cells are positive for CD56{top left} and TIA-1{top right}.

HISTOMOROPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS GAMMA DELTA T CELL LYMPHOMA.

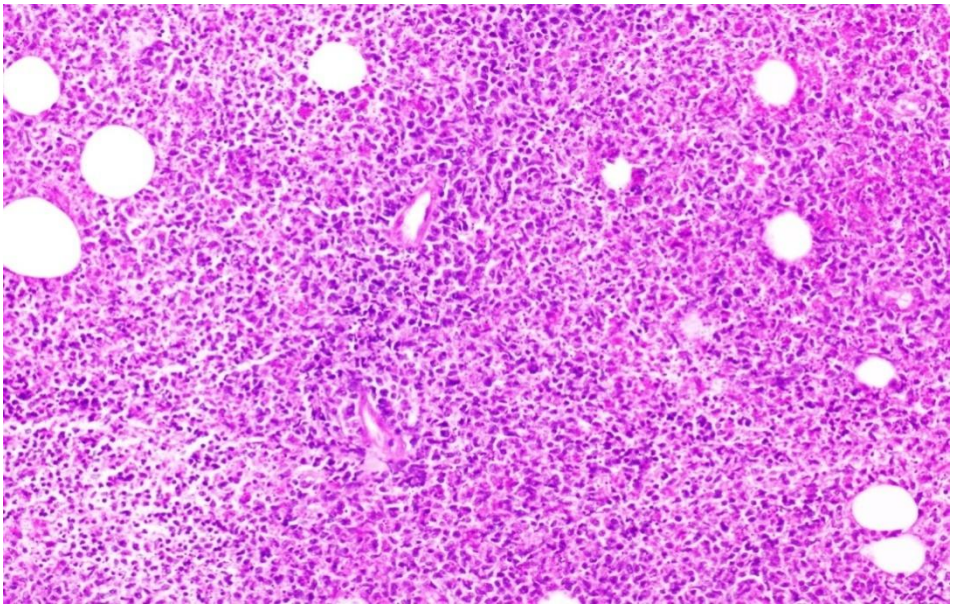


Figure 21: Primary cutaneous Gamma Delta T cell lymphoma: Shows diffuse atypical lymphoid infiltrate with preserved subcutis adipocytes and few small calibre thin walled ectatic blood vessels. H&E 100x

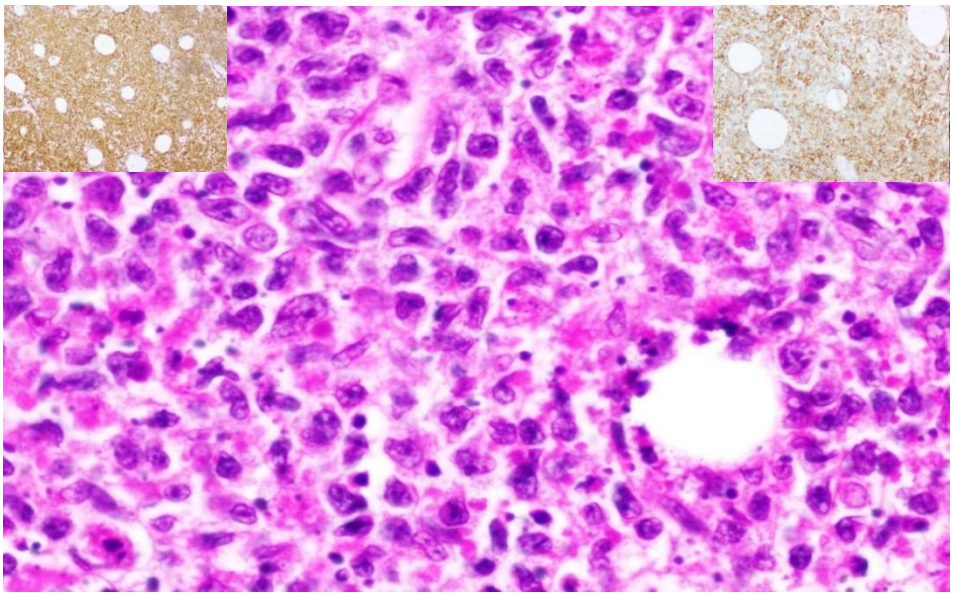


Figure 22:Primary cutaneous Gamma Delta T cell lymphoma: Shows medium to large sized atypical lymphoid cells with round to ovoid nuclei, hyperchromatic to vesicular chromatin, irregularity in nuclear membrane and scant to moderate amounts of cytoplasm admixed wit nuclear dust{H&E 400x}. Inset pictures {top left=CD3, top right= CD56}.

HISTOMOROPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS SMALL MEDIUM SIZED PLEOMORPHIC T CELL LYMPHOMA.

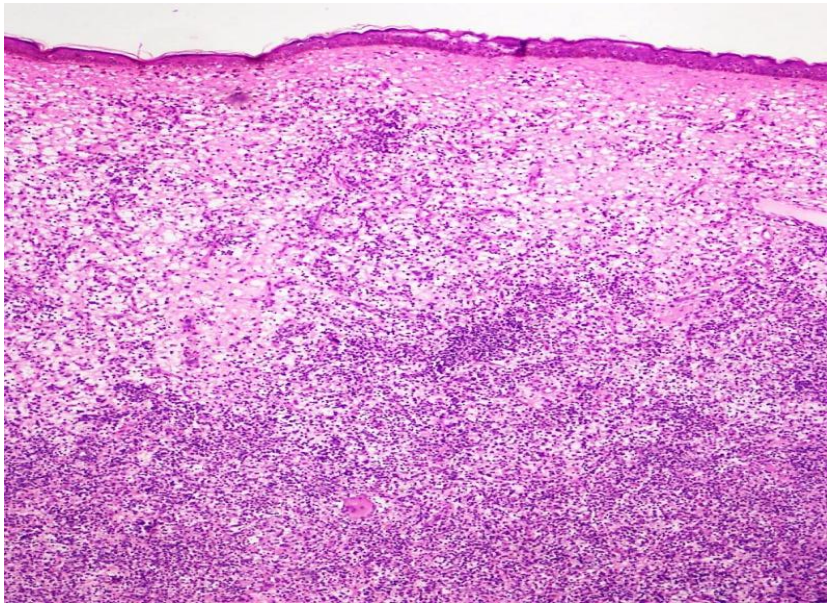


Figure 23: Primary cutaneous small medium sized pleomorphic T cell lymphoma: Shows dermal infiltrates of atypical cells with atrophy of epidermis. H&E 40x

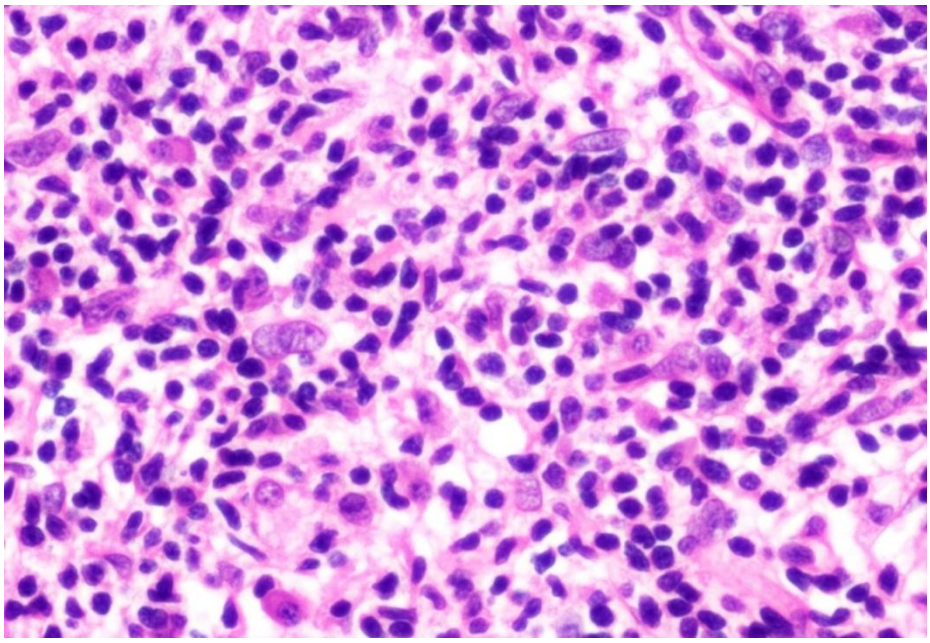


Figure 24: Primary cutaneous small medium sized pleomorphic T cell lymphoma: Shows small to medium sized atypical lymphoid cells with hyperchromatic nuclei and scant cytoplasm with few admixed large histiocytes. H&E 400x

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS DIFFUSE LARGE B CELL LYMPHOMA, OTHER.

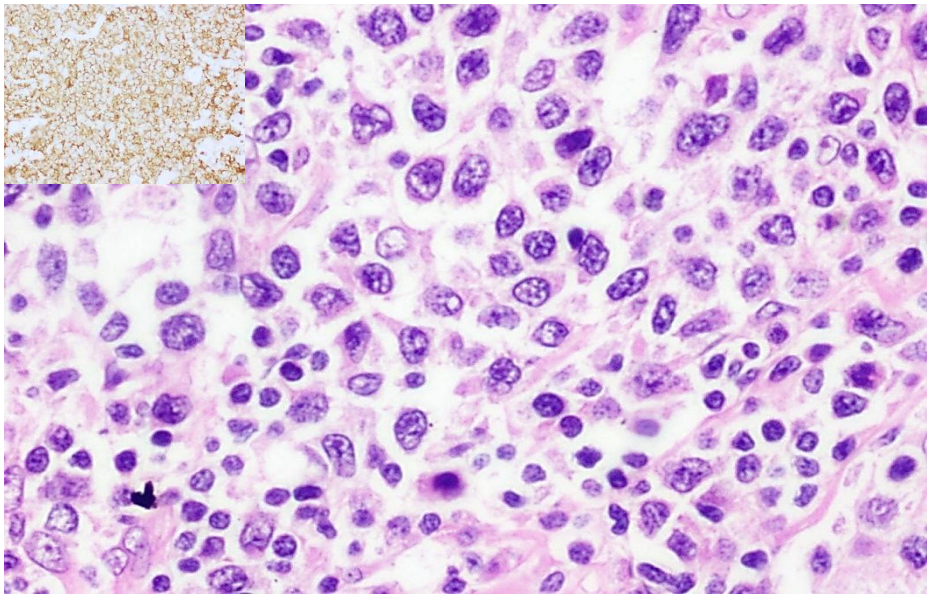


Figure 25: Primary cutaneous diffuse large B cell lymphoma, other: Shows medium to large sized cells with centrocytes, few centroblasts, occasional immunoblast and few intermixed mature lymphocytes {H&E 400x}. Inset {top left} shows CD20 positive tumor cells.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA.

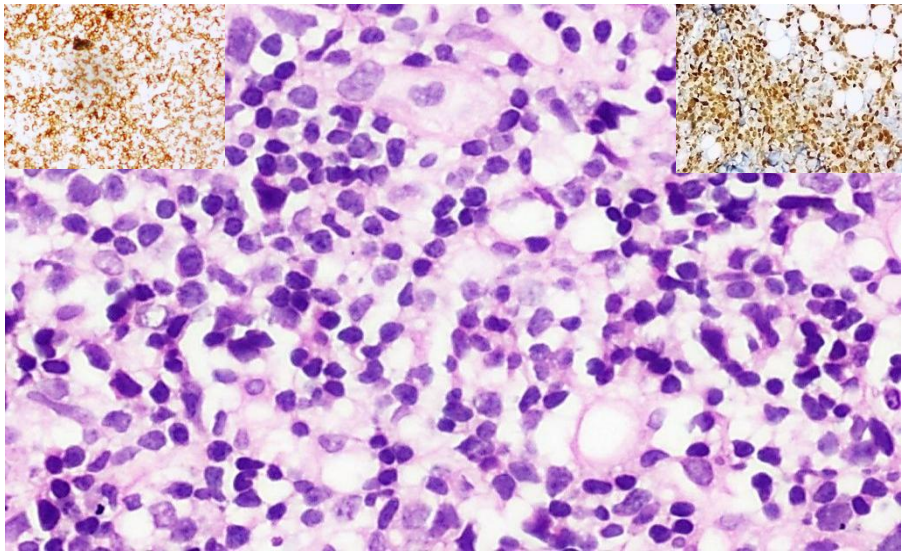


Figure 26: Acute lymphoblastic leukemia/lymphoma: Shows atypical lymphoid infiltrate with round to oval hyperchromatic nuclei, inconspicuous nucleoli, mild nuclear irregularity and scant cytoplasm {H&E 400x }. Inset pictures show CD3 {top left} and TdT positive {top right} tumor cells.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA.

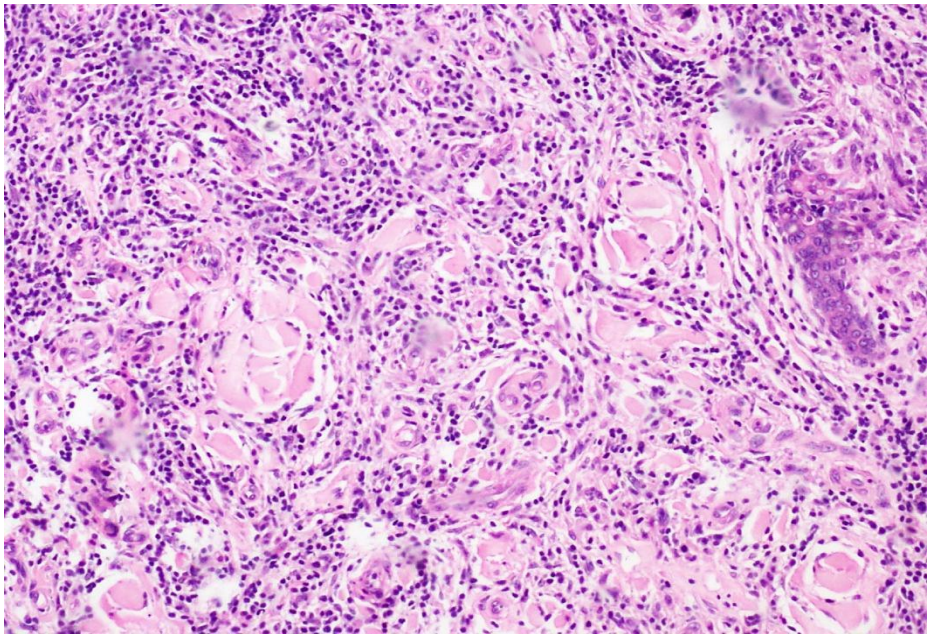


Figure 27: Primary cutaneous marginal zone lymphoma: Shows atypical small lymphoid infiltrate in dermis with seperation of collagen. H&E 100x

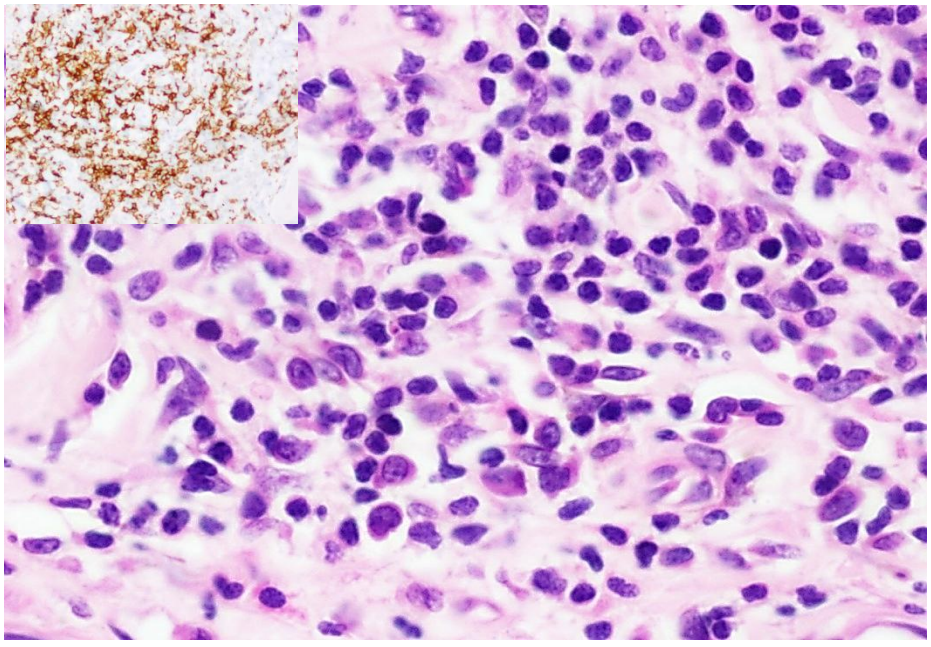


Figure 28: Primary cutaneous marginal zone lymphoma: Shows atypical small to medium sized lymphoid cells with few plasmacytoid cells and occasional plasma cells {H&E 400x}. Inset picture shows the atypical cells are positive for CD20.

HISTOMORPHOLOGY AND IMMUNOHISTOCHEMISTRY OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM.

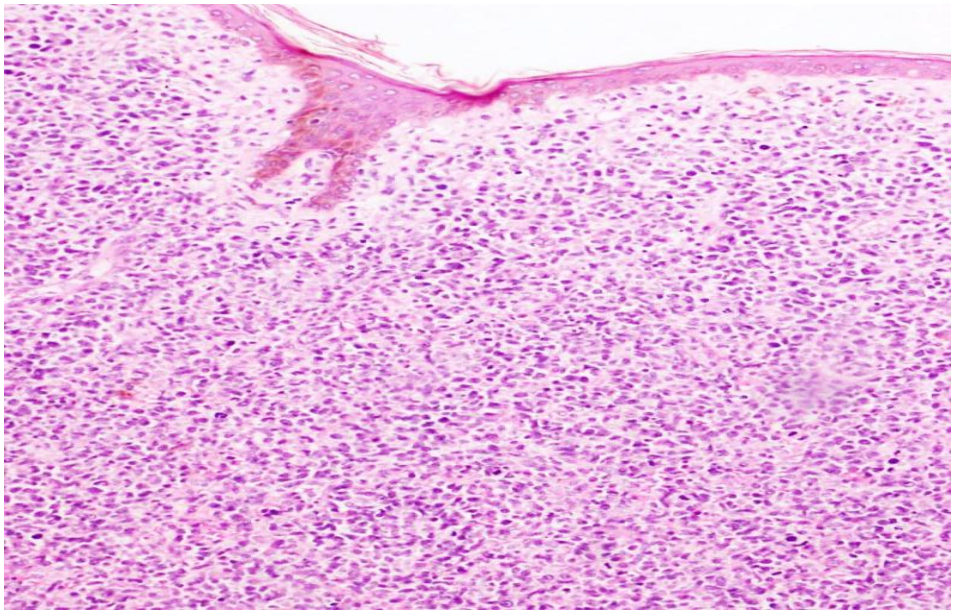


Figure 29: Blastic plasmacytoid dendritic cell neoplasm: Shows diffuse dermal infiltates of atypical small cells with epidermal atrophy. H&E 100x

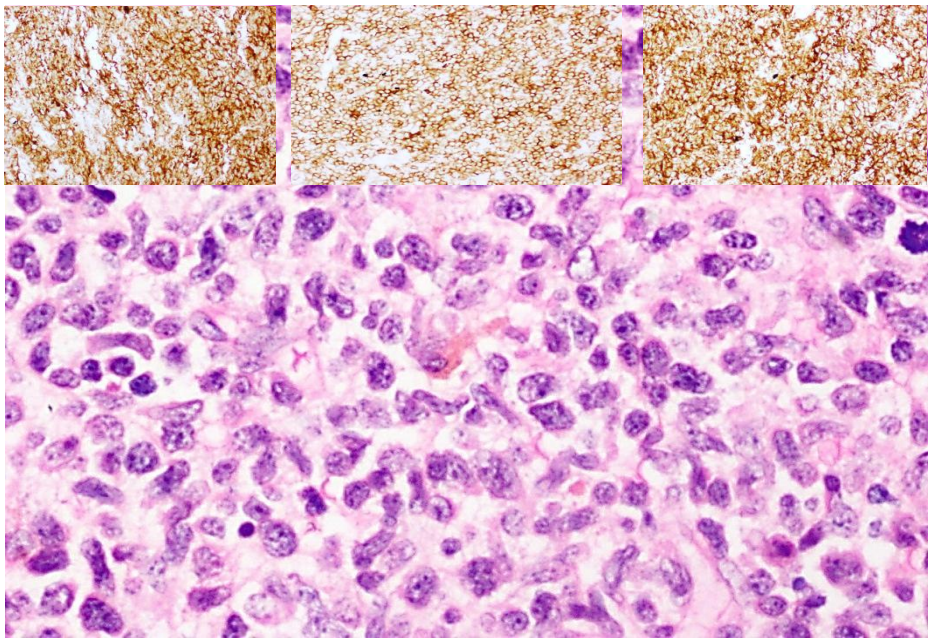


Figure 30: Blastic plasmacytoid dendritic cell neoplasm: Shows predominantly medium sized cells with oval to elongated nuclei, mild nuclear irregularity with few cells having folding, coarse chromatin and few cells with small nucleoli and scant amounts of cytoplasm{H&E 400x}. Inset pictures show tumor cells are positive for CD4{top left}, CD56{top right}and CD123{top middle}.

IMMUNOHISTOCHEMISTRY FOR NOTCH-1.

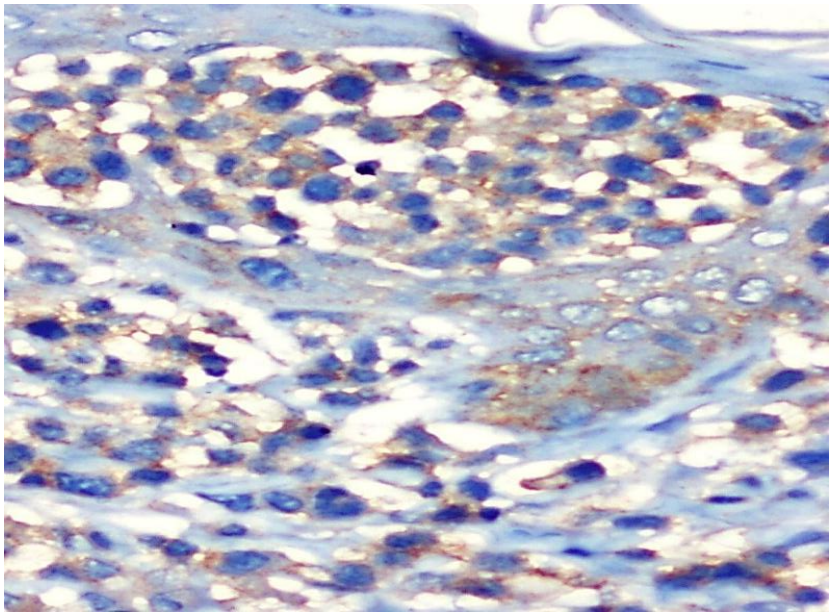


Figure 31: Mycosis Fungoides in Transformation: Cytoplasmic and membranous weak positivity of Notch-1 in Mycosis fungoides Transformation case. ICC Notch-1 400x

IMMUNOHISTOCHEMISTRY FOR FOX P1.

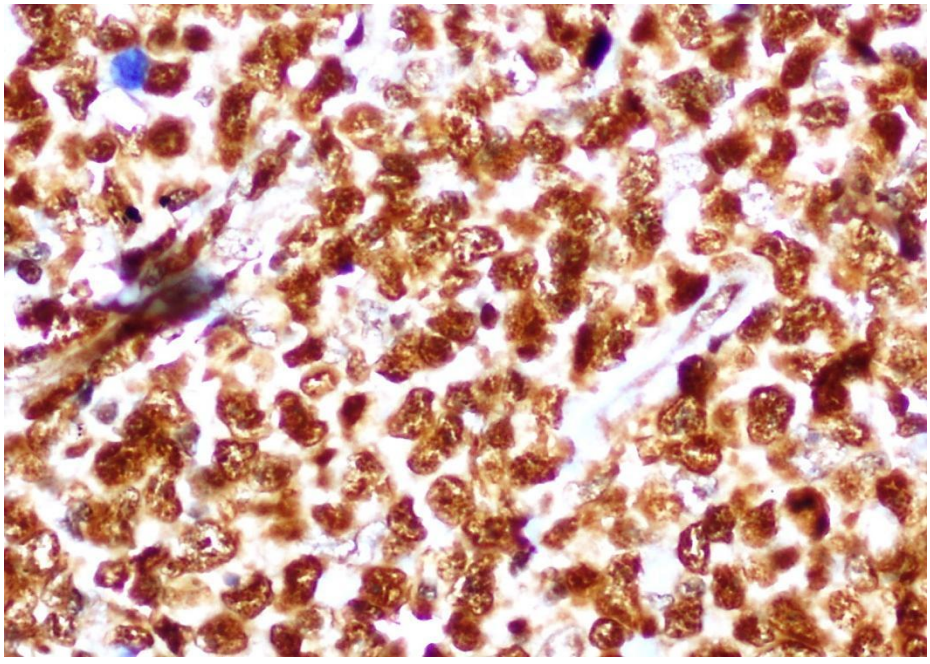


Figure 32: Immunohistochemistry for Fox p1 shows diffuse and nuclear positivity for Fox p1 in diffuse large B cell lymphoma, other. More or less round cell morphology is also appreciated. ICC400x.

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APPENDICES

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APPENDIX 1: PROCESSING OF TISSUES FOR HISTOPATHOLOGICAL EXAMINATION

Automated processor was used with twelve jars. Processing time was thirteen hours.

1. Dehydration: Carried out in the first seven jars containing increasing gradations of alcohol starting from 70%, 80%, 90% and 95% followed by three changes in absolute alcohol. The total duration was eight hours.
2. Clearing: Three changes in toluene for one hour each.
3. Impregnation: Two changes in paraffin wax at 65^{o}centigrade, one hour each.

APPENDIX 2: PANEL OF ANTIBODIES USED IN IMMUNOHISTOCHEMISTRY [IHC]

Sl Num.	Antibody	Marker	Clone	Source**	Dilution	Pre-treatment*
1	CD3	Pan T cell	F 7.2.38	D	1:750	EDTA
2	CD20	Pan B cell	L26	D	1:500	CITRATE
3	CD5	Pan T cell	4C7(N)	N	1:50	EDTA
4	CD7	Pan T cell	CBC.37	D	1:25	EDTA
5	CD4	Helper cell	SP35	V	1:80	EDTA
6	CD8	Cytotoxic cell	T C8144/B	D	1:50	EDTA
7	CD56	NK antigen	cell 123 C3	N	1:50	CITRATE
8	CD10	Germinal Centre	56C6	N	1:10	EDTA
9	CD21	FDC	1F8	D	1:25	TRYPSIN
10	CD23	FDC	IB12	D	1:10	EDTA
11	CD30	Activation marker	BER H2	D	1:50	EDTA
12	ALK		ALK1	D	1:50	EDTA
13	TIA-1	Cytotoxic granule	TIA-1	AB	1:100	EDTA
14	GRANZ B	Cytotoxic granule	Gr B7	D	1:50	EDTA
15	LMP-1	EBV	CS. 1-4	D	1:100	EDTA
16	Bcl2		ST D40	D	1:25	EDTA
17	Bcl6	Germinal Centre	ST D40	D	1:50	EDTA
18	MIB 1	Proliferative index	MIB 1	D	1:100	EDTA
19	Notch 1	Activation marker	EP1238Y	AB	1:100	EDTA
20	Fox p1		JC 12	AB	1:50	Citrate

* Citrate at pH6, EDTA at pH8 Pressure cooking for 30 sec at a temperature of 120 degrees centigrade and pressure of 15 psi.

** (D – DAKO; N – NOVA CASTRA, AB – ABCAM)

LMP-1: Latent membrane protein; FDC: Follicular dendritic cell; ALK: Anaplastic lymphoma kinase; EMA: Epithelial membrane antigen; TIA-1: T cell restricted intracellular antigen; Granz B: Granzyme B

APPENDIX 3: TECHNIQUE OF MANUAL IMMUNOHISTOCHEMISTRY BY ENVISION/2STEP POLYMER METHOD.

1. Approximately three microns thick sections were cut and floated on poly-Llysine coated slides and incubated 37 degrees centigrade overnight. An appropriate control was used for the antibody tested.
2. Sections were dewaxed in xylene for 15 minutes and brought to water.
3. Antigen retrieval was done by heat induced pressure cooking

   a. Slides depending on the IHC antibody used were placed in the container containing either citrate buffer at pH 6 or EDTA buffer at pH 9 and placed in the cooker with lid closed for 30 seconds at a temperature of 120 degrees centigrade and a pressure of 15 psi.

   b. After boiling, the cooker was cooled by quenching in a sink of cold running tap water.

4. The slides were removed from the cooker, quickly washed in running tap water and transferred to TRIS buffered saline {TBS} at pH 7.6
5. 0.3% Hydrogen peroxide {H2O2} was added to the slide and incubated at room temperature for 10 min to block endogenous peroxidase.
6. The slides were washed in TBS at pH 7.6
7. The primary antibody was applied and incubated at room temperature for 30 minutes.
8. The slides were washed in TBS at pH 7.6
9. Envision {commercially available secondary antibody + enzyme} was applied and incubated at room temperature for 30 minutes.
10. The slides were washed in TBS at pH 7.6
11. Chromogen {Diaminobenzidine} along with substrate {hydrogen peroxide} was applied.
12. Slides were washed in running tap water.
13. The slides were counterstained with Harris haematoxylin for 10 seconds and then dehydrated, cleared and mounted.

APPENDIX 4: PREPARATION OF REAGENTS USED FOR IMMUNOHISTOCHEMISTRY

1. TBS {TRIS from Aldrich}. The pH is checked and adjusted to 7.6

Nacl	80g
TRIS	6.05g
1N HCl	40ml
Distilled H2O	10 litres

2. Hydrogen peroxide – H_2O_2 is available commercially as 30% solution from Qualigens {SQ}. A 0.3% solution is prepared by adding 1 ml of H_2O_2 to 9 ml of distilled water.
3. DAB solution – Commercially available 5 ml solution from DAKO along with 250 ml of substrate buffer. Working solution is prepared by mixing DAB solution and substrate buffer in a ratio of 1:50.

APPENDIX 5: CELL SURFACE CD MOLECULES THAT ARE PREFERENTIALLY EXPRESSED BY T CELLS.

ICC MARKER	EXPRESSED ON	POSITIVE FOR (USEFUL PRIMARY IN LYMPHOMA)	GENE OR SIGNAL PATHWAY	PARTICULAR NOTE	ALSO POSITIVE IN OTHER TUMORS
CD2	Pan T cell , few thymic B cells, NK cell	Majority of T cell lymphomas	Surface protein complex	--	NK cell malignancies
CD3	Pan T cell	T cell lymphomas	T cell receptor binds to CD3 protein complex	Most specific (>90%)	NK cells (cytoplasmic CD56)
CD4	Helper induced subset of T cells	Post thymic T cell leukemia/lymphoma	Binds to HLA class II	Absent on immature thymocytes	Dendritic/histiocyticneoplasm, AML(M4,M5)
CD5	Pan T cell, Few subset of circulating B cells	Most T cell lymphomas	Signal transduction molecule on thymocyte and immature T cell	--	CLL*, MCL*, thymic carcinoma

CD7	Pan T cell	Lost in PTCL	Membrane expression, immunoglobulin family	--	NK cell neoplasm, CML
CD8	suppressor/cytotoxic T cell subset, cortical thymocytes	TCL(post thymic)	Cell surface glycoprotein	--	NK/T cell lymphoma, Melanoma
CD30	Activated lymphocyte marker,	CD30 LPD	TNF receptor family	Membranous and Golgi type staining	Classical HL*, melanoma, germ cell tumor
ALK-1	Expression is upregulated by fusion of ALK to the NPM gene	ALCL	Protein product of ALK kinase	T(2:5)	IMT*, RMS*, rare DLBCL
TIA-1	NK cells and cytotoxic T lymphocytes(unstimulated)	SPTCL, NK/T cell	Cytotoxic granule associated protein	Not expressed by thymocytes	Large granular TCL, hepatosplenic TCL
Perforin/ GranzymeB	Expressed by CD3-, CD16+ NK cells and γδ T cells.	SPTCL(gamma-delta), NK/T CL	cytotoxic granule associated proteins	--	Hemophagocytic syndrome
CD56	NK cells	NK/T cell lymphoma, blastic/plasmacytoid dendritic cell neoplasm, gamma-delta TCL	Glycoprotein with cell to cell adhesion	Expressed in CD4&CD8 subsets	Neuroblastoma, myeloma, AML, neuroendocrine tumor, EATCL*
CD57	NK cell, T cell subset in germinal center	As above	Glycoprotein with cell adhesion	--	Neuroendocrine tumor. High grade prostatic adenocarcinoma
CD10, BCL-6, PD-1	Follicular T helper cell antigen	PCFCL(BCL 2-negative), ALL(CD10 positive), PCDLBCL	--	--	AITCL*, ALL

*CLL : Chronic lymphocytic leukemia, MCL : Mantle cell lymphoma, IMT : Inflammatory myofibroblastic tumor, RMS : Rhabdomyosarcoma, AITCL : Angioimmunoblastic T cell lymphoma, EATCL: Enteropathy associated T cell lymphoma.—(**Adapted from Dabb's textbook of Immunohistochemistry)**

APPENDIX 6: CELL SURFACE CD MOLECULES THAT ARE PREFERENTIALLY EXPRESSED BY B CELLS

Name	Original names	Cellular reactivity	Structure
CD19	B4	PanB cell, FDCs?	Igsuperfamily
CD20	B1	Mature B cells	MS4A family
CD21	B2, HB-5	Mature B cells, FDCs	Complement receptor family
CD22	BL-CAM, Lyb-8	Mature B cells	Ig superfamily
CD23	FcεRII	Activated B cells, FDCs, others	C type Lectin
CD24	BA-1, HB6	Pan-B cell, granulocytes, epithelial cells	GPI Anchored
CD40	Bp50	B cells, epithelial cells, FDCs, others	TNF receptor
CD72	Lyb-2	PanB cell	C-type lectin
CD79a,b	Igα,β	Surface Ig positive B cells	Ig superfamily

FDCs: follicular dendritic cells. (Adapted from**: B lymphocytes: how they develop and function, LeBien**)

APPENDIX 7: WHO-EORTC CLASSIFICATION OF CUTANEOUS LYMPHOMA.

Cutaneous T and NK cell lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma*
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous Bcell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other Intravascular large B-cell lymphoma
Precursor hematologic neoplasm
CD4/CD56 positive hematodermic neoplasm (Blastic NK-cell lymphoma)†

Adapted from article published in Blood by Willemze et al. in 2005.

APPENDIX 8: CLINICAL STAGING SYSTEM FOR MYCOSIS FUNGOIDES AND SEZARY SYNDROME, AS RECENTLY PROPOSED BY ISCL-EORTC

Stage I	Disease confine to the skin with patches or papules or plaques less than 10% (IA) or greater than 10% (IB) of the skin surface; no clinically abnormal lymphnode.
Stage II	Skin involvement with patches or papules or plaques associated with early (N1-N2) lymph node involvement (IIA) or skin involvement with one or more tumors {more than 1cm}(IIB)
Stage III	Skin involvement with erythroderma, no or early lymph node involvement (N1-N2) and absent or low blood tumor burden (less than 1000/µl circulating Sézary cells).
Stage IV	High blood tumor burden (more than 1000/µl circulating Sézary cells) and/or extensive lymph node involvement (N3) or visceral involvement (M1).

Histopathological staging for clinically abnormal lymph node (more than 1.5cm) in MF/SS

ISCL EORTC	Dutch system	NCI classification
N1	Category 1: DL, no atypical CMC	LN0: no atypical lymphocytes
		LN1: occasional, isolated atypical lymphocytes
		LN2: clusters(3-6) of atypical lymphocytes
N2*	Category 2: DL with early involvement with scattered atypical CMC	LN3: aggregates of atypical lymphocytes, but architecture preserved
N3	Category 3: partial effacement of architecture with many CMC	LN4: partial or complete effacement of architecture with many atypical lymphocytes
	Categroy 4: complete effacement of architecture	

*****N2 is divided into N2a (without clonally rearranged T cells and N2b (with clonally rearranged T cells). DL: dermatopathic lymphadenopathy; CMC: cerebriform mononuclear cells with nuclei >7.5µ.

(Adapted from: Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al.Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007 Sep 15;110(6):1713-22).

APPENDIX 9: ALGORITHM FOR THE DIAGNOSIS OF EARLY MF

Criteria	Major (2 points)	Minor (1 point)
Clinical		
Persistent and/or progressive patches and plaques plus	Any 2	Any 1
(1) Non–sunexposed location		
(2) Size and/or shape variation		
(3) Poikiloderma		
Histopathologic		
Superficial lymphoid infiltrate plus	Both	Either
(1) Epidermotropism without spongiosis		
(2) Lymphoid atypia*		
Molecular and/or biologic: clonal TCR gene rearrangement	NA†	Present
Immunopathologic		
(1) CD2,3,5 less than 50% of T cells	NA†	Any 1
(2) CD7 less than 10% of T cells		
(3) Epidermal discordance from expression of CD2,3,5 or CD7 on dermal T cells		

- — indicates not applicable.
- * Lymphoid atypia is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours.
- † Not applicable since it cannot fulfill any major criteria.-- **(Adated from: Pimpinelli:-Defining early MF)**

APPENDIX 10: ANN ARBOR STAGING OF LYMPHOMAS

Stage I	Involvement of single lymph node region or lymphoid structure{spleen, thymus, Waldeyer's ring}
Stage II	Involvement of two or more lymph node regions on the same side ofthe diaphragm
Stage III	Involvement of lymph nodes regions on both sides of diaphragm.
Stage IV	Involvement of extra nodal site or sites beyond those designated in E.

For all stages the following descriptors are used

E: Involvement of site, extra nodal site contiguous or proximal to known nodal site.

A: No symptoms

B: Fever {38^{o}C}, drenching sweats, weight loss {10% body weight more than 6 months}.

S: Splenomegaly--**(Adapted from: Armitage JO. Staging non-Hodgkin lymphoma. CA Cancer J Clin. 2005 Nov-Dec;55(6):368-76.)**

APPENDIX 11: INTERNATIONAL PROGNOSTICATION INDEX

The following factors are assigned a score of 1 each and the risk category calculated.

Age	More than 60 years
Serum LDH	More than 1 x normal
ECOG performance status	2 to 4
Ann Arbor stage	III or IV
Extranodal involvement	More than 1 site

Calculation of risk categories

Low	0 or 1
Low intermediate	2
High intermediate	3
High	4 or 5

Performance status - Eastern Cooperative Oncology Group scale {ECOG}

0	Patient has no symptoms
1	Ambulatory patient with symptoms
2	Bedridden patient for < half a day
3	Bedridden patient for half a day or more
4	Chronically bedridden with assistance required for daily activities

--(Adapted from: **Hermans J, Krol AD, van Groningen K, Kluin PM, Kluin-Nelemans JC, Kramer MH, et al. International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. Blood. 1995 Aug 15;86(4):1460-3,)(A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993 Sep 30;329(14):987-94**)

APPENDIX 12: COMPARISON BETWEEN WHO-EORTC CLASSIFICATION 2005(Willemze)AND 2008(Olsen).

WHO-EORTC 2005	WHO-EORTC 2008
Cutaneous Tcell and NKcell lymphomas	**Cutaneous Tcell and NKcell lymphomas**
Mycosis fungoides	Mycosis fungoides
MF variants and subtypes	MF variants and subtypes
Folliculotropic MF	Folliculotropic MF
Pagetoid reticulosis	Pagetoid reticulosis
Granulomatous slack skin	Granulomatous slack skin

Sézary syndrome	Sézary syndrome
Adult Tcell leukemia/lymphoma	Adult Tcell leukemia/lymphoma
Primary cutaneous CD30 positive lymphoproliferative disorders	Primary cutaneous CD30 positive lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis	Lymphomatoid papulosis
Subcutaneous panniculitislike Tcell lymphoma	Subcutaneous panniculitislike Tcell lymphoma
Extranodal NK/Tcell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral Tcell lymphoma, unspecified	Primary cutaneous peripheral Tcell lymphoma, rare subtypes
Primary cutaneous aggressive epidermotropic CD8 positive Tcell lymphoma (provisional)	Primary cutaneous aggressive epidermotropic CD8 positive Tcell lymphoma (provisional)
Cutaneous gamma/delta Tcell lymphoma (provisional)	Cutaneous gamma/delta T-cell lymphoma (provisional)
Primary cutaneous CD4 positive small/medium sized pleomorphic T-cell lymphoma (provisional)	Primary cutaneous CD4 positive small/medium sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas	**Cutaneous B-cell lymphomas**
Primary cutaneous marginal zone Bcell lymphoma	Primary cutaneous marginal zone Bcell lymphoma
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large Bcell lymphoma, leg type	Primary cutaneous diffuse large Bcell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other Intravascular large B-cell lymphoma	*(Primary cutaneous) Intravascular large B-cell lymphoma*
Precursor hematologic neoplasm	**Precursor hematologic neoplasm**
CD4 positive/CD56 positive hematodermic neoplasm (blastic NKcell lymphoma)†	*Blastic plasmacytoid dendritic cell neoplasm*

APPENDIX 13: IMMUNOPHENOTYPING FEATURES OF T AND NK CELL LYMPHOMA

Cutaneous T/NK cell lymphomas	Subtypes	CD2	CD3	CD4	CD5	CD7	CD8	CD30	CD45RO	CD56
MF	Patch	+	+	+ > –	+	+/–	– > +	–	+	–
	Plaque	+	+	+ > –	+	+/–	– > +	–	+	–
	Tumor	+/–	+/–	+ > –	+/–	– > +	– > +	– > +	+/–	–
	Erythrodermic	+	+	+ > –	+	– > +	– > +	–	+	–
	Follicular mucinosis	+	+	+ > –	+	+	– > +	–	+	–
	Pagetoid reticulosis		+	+/–	+	+/–	+/–	+/–	+/–	–
	Granulomatous slack skin		+	+		– > +	–	–		–
SS			+	+	+	+/–	–	–	+	–
Large T cell lymphoma	CD30–	+/–	+/–	+	+/–		–	–		–
	CD30+	+/–	+/–	+ > –	+/–		–	+		
LyP	Types A, C	+/–	+	+ > –	+/–		–	+		–
	Type B		+	+			–	–		–
Angio centric lymphoma		+	+/–	+/–	+/–	+/–	+/–			+/–
SPTCL			+	+/–	+/–	+/–	+/–			– > +
ATL		+	+	+ > –	+	–	– > +			–
PTL		+/–	+ > –	+ > –	+ > –	–	– > +	– > +		– > +

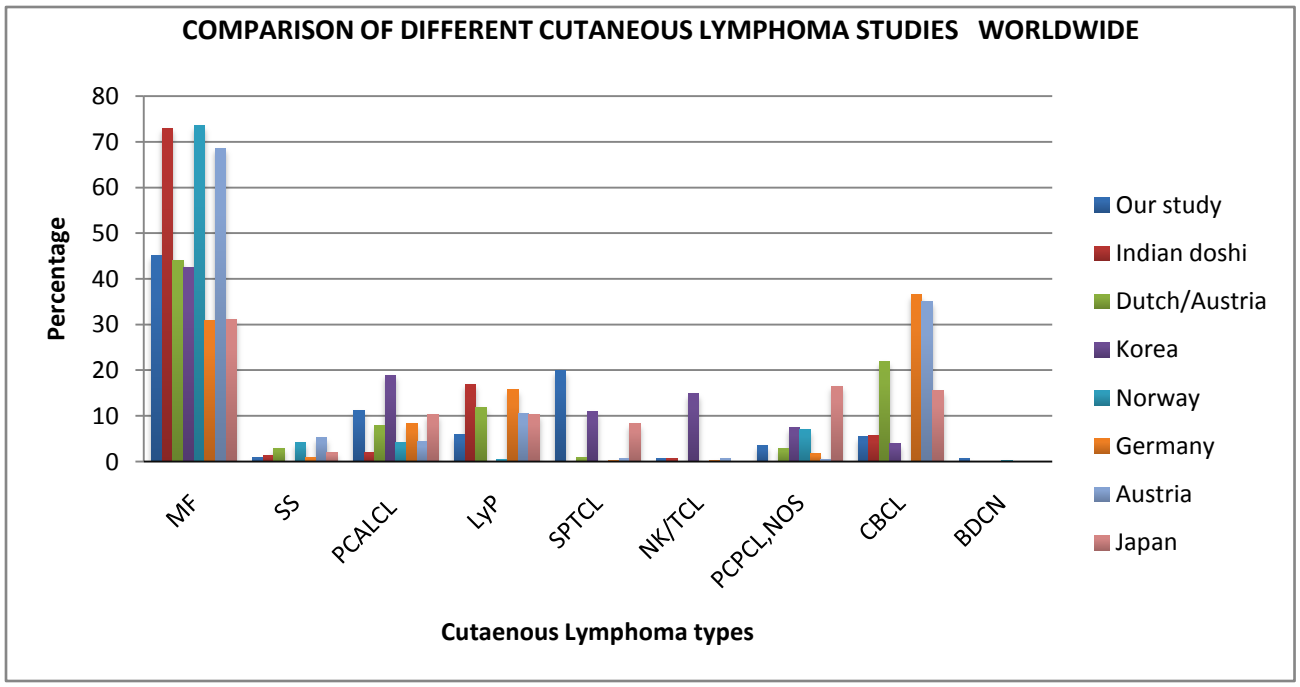
+, Positive; –, negative; ALK, anaplastic lymphoma kinase; MF: Mycosis Fungoides, SS: Sézary syndrome, Lyp: Lymphomatoid Papulosis, SPTCL: Subcutaneous panniculitis like T cell lymphoma, ATL : Adult T cell leukemia/lymphoma, PTL: Pleomorphic T cell lymphoma.

APPENDIX 14: **IMMUNOPHENOTYPING FEATURES OF B CELL LYMPHOMA**

Cutaneous B cell lymphoma	CD5	CD10	CD19	CD20	CD21	CD23	CD30	CD43	CD79a
MZL	–	– > +	+	+ > –		– > +		+/–	+
Immunocytoma	–	–	+	+ > –		–		+/–	
FCL	–	–	+	+		– > +		–	+
LBCL	– > +	– > +	+	+			–		+
CLL/SLL	+ (f), +/-(p)	–	+	+		+		+	+
Plasmacytoma			–	–			+/–	+/–	+/–

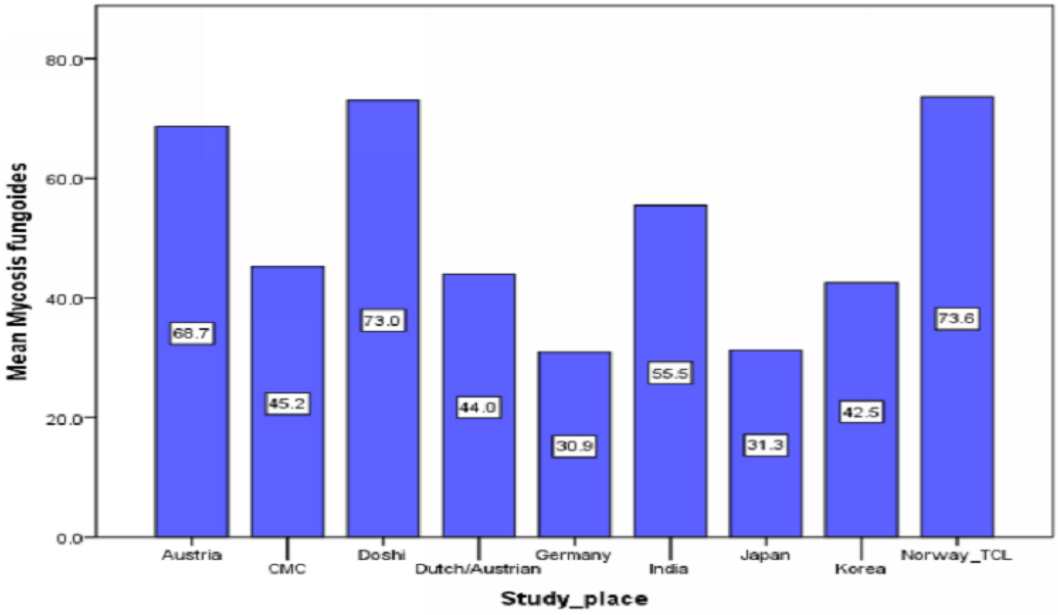
+ Positive; – Negative; f, frozen tissue; p, paraffin-embedded, formalin-fixed tissue; MZL: Marginal Zone lymphoma ; FCL: Follicle center lymphoma ; LBCL:Large B cell lymphoma ; CLL/SLL: Chronic lymphocytic leukemia/Small lymphocytic lymphoma. BOTH TABLES ADAPTED FROM --Jane M. Grant-Kels MAF.Practical evaluation and management of cutaneous lymphoma. J Am AcadDermatol 2002;46:325-57). 46(2002):325–57.

Appendix 15: COMPARISON OF CUTANEOUS LYMPHOMA STUDIES WORLDWIDE.



MF: Mycosis Fungoides; SS: Sézary syndrome; PCALCL: Primary cutaneous anaplastic large cell lymphoma; LyP: Lymphomatoid Papulosis; SPTCL: Subcutaneous panniculitis like T cell lymphoma; NK/TCL: Extra nodal NK/T cell lymphoma, nasal type; PCPCL, NOS: Primary cutaneous peripheral cell lymphoma, others; CBCL; Cutaneous B cell lymphoma; BDCN: Blastic dendritic cell neoplasm.

Appendix 16:COMPARSION OF MYCOSIS FUNGOID FREQUENCY WITH PREVIOUS INDIAN STUDY AND WITH DIFFERENT REGIONS OF WORLD.



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Additional Vice Principal (Research)

April29, 2013

Dr. Jigar Kirikumar Shah
PG Registrar
Department of General Pathology
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
A 5 year retrospective study of spectrum of cutaneous lymphomas presenting to tertiary care centre.
Dr. Jigar Kirikumar Shah, PG Registrar, General Pathology, Dr. Meera Thomas, General Pathology, Dr. Susanne Abraham, Dermatology, Venereology and Leprosy.

Ref: IRB Min. No. 8247 dated 19.03.2013

Dear Dr. Jigar Kirikumar Shah,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Meera Thomas, Department of General Pathology, CMC

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April 29, 2013

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Ref: IRB Min. No. 8247 dated 19.03.2013

Dear Dr. Jigar Kirikumar Shah,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A 5 year retrospective study of spectrum of cutaneous lymphomas presenting to tertiary care centre." on March 19, 2013.

The Committees reviewed the following documents:

1. Format of IRB application
2. Information Sheet and Consent Form (English)
3. Proforma
4. Cvs of Drs. Jigar Kirikumar Shah, Meera Thomas, Susanne Abraham.
5. A CD containing documents 1 – 4.

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